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(54) Title: KINASES AND PHOSPHATASES

(57) Abstract: The invention provides human kinases and phosphatases (KAP) and polynucleotides which identify and encode KAP. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with aberrant expression of KAP.

## KINASES AND PHOSPHATASES

### TECHNICAL FIELD

5        This invention relates to nucleic acid and amino acid sequences of kinases and phosphatases and to the use of these sequences in the diagnosis, treatment, and prevention of cardiovascular diseases, immune system disorders, neurological disorders, disorders affecting growth and development, lipid disorders, cell proliferative disorders, and cancers, and in the assessment of the effects of exogenous compounds on the expression of nucleic acid and amino acid sequences of  
10 kinases and phosphatases.

### BACKGROUND OF THE INVENTION

Reversible protein phosphorylation is the ubiquitous strategy used to control many of the intracellular events in eukaryotic cells. It is estimated that more than ten percent of proteins active  
15 in a typical mammalian cell are phosphorylated. Kinases catalyze the transfer of high-energy phosphate groups from adenosine triphosphate (ATP) to target proteins on the hydroxyamino acid residues serine, threonine, or tyrosine. Phosphatases, in contrast, remove these phosphate groups. Extracellular signals including hormones, neurotransmitters, and growth and differentiation factors can activate kinases, which can occur as cell surface receptors or as the activator of the final  
20 effector protein, as well as other locations along the signal transduction pathway. Cascades of kinases occur, as well as kinases sensitive to second messenger molecules. This system allows for the amplification of weak signals (low abundance growth factor molecules, for example), as well as the synthesis of many weak signals into an all-or-nothing response. Phosphatases, then, are essential in determining the extent of phosphorylation in the cell and, together with kinases, regulate  
25 key cellular processes such as metabolic enzyme activity, proliferation, cell growth and differentiation, cell adhesion, and cell cycle progression.

#### KINASES

Kinases comprise the largest known enzyme superfamily and vary widely in their target molecules. Kinases catalyze the transfer of high energy phosphate groups from a phosphate donor  
30 to a phosphate acceptor. Nucleotides usually serve as the phosphate donor in these reactions, with most kinases utilizing adenosine triphosphate (ATP). The phosphate acceptor can be any of a variety of molecules, including nucleosides, nucleotides, lipids, carbohydrates, and proteins. Proteins are phosphorylated on hydroxyamino acids. Addition of a phosphate group alters the local charge on the acceptor molecule, causing internal conformational changes and potentially  
35 influencing intermolecular contacts. Reversible protein phosphorylation is the primary method for

regulating protein activity in eukaryotic cells. In general, proteins are activated by phosphorylation in response to extracellular signals such as hormones, neurotransmitters, and growth and differentiation factors. The activated proteins initiate the cell's intracellular response by way of intracellular signaling pathways and second messenger molecules such as cyclic nucleotides, calcium-calmodulin, inositol, and various mitogens, that regulate protein phosphorylation.

Kinases are involved in all aspects of a cell's function, from basic metabolic processes, such as glycolysis, to cell-cycle regulation, differentiation, and communication with the extracellular environment through signal transduction cascades. Inappropriate phosphorylation of proteins in cells has been linked to changes in cell cycle progression and cell differentiation. Changes in the cell cycle have been linked to induction of apoptosis or cancer. Changes in cell differentiation have been linked to diseases and disorders of the reproductive system, immune system, and skeletal muscle.

There are two classes of protein kinases. One class, protein tyrosine kinases (PTKs), phosphorylates tyrosine residues, and the other class, protein serine/threonine kinases (STKs), phosphorylates serine and threonine residues. Some PTKs and STKs possess structural characteristics of both families and have dual specificity for both tyrosine and serine/threonine residues. Almost all kinases contain a conserved 250-300 amino acid catalytic domain containing specific residues and sequence motifs characteristic of the kinase family. The protein kinase catalytic domain can be further divided into 11 subdomains. N-terminal subdomains I-IV fold into a two-lobed structure which binds and orients the ATP donor molecule, and subdomain V spans the two lobes. C-terminal subdomains VI-XI bind the protein substrate and transfer the gamma phosphate from ATP to the hydroxyl group of a tyrosine, serine, or threonine residue. Each of the 11 subdomains contains specific catalytic residues or amino acid motifs characteristic of that subdomain. For example, subdomain I contains an 8-amino acid glycine-rich ATP binding consensus motif, subdomain II contains a critical lysine residue required for maximal catalytic activity, and subdomains VI through IX comprise the highly conserved catalytic core. PTKs and STKs also contain distinct sequence motifs in subdomains VI and VIII which may confer hydroxyamino acid specificity.

In addition, kinases may also be classified by additional amino acid sequences, generally between 5 and 100 residues, which either flank or occur within the kinase domain. These additional amino acid sequences regulate kinase activity and determine substrate specificity. (Reviewed in Hardie, G. and S. Hanks (1995) The Protein Kinase Facts Book, Vol I, pp. 17-20 Academic Press, San Diego CA.). In particular, two protein kinase signature sequences have been identified in the kinase domain, the first containing an active site lysine residue involved in ATP binding, and the second containing an aspartate residue important for catalytic activity. If a protein analyzed

includes the two protein kinase signatures, the probability of that protein being a protein kinase is close to 100% (PROSITE: PDOC00100, November 1995).

### Protein Tyrosine Kinases

Protein tyrosine kinases (PTKs) may be classified as either transmembrane, receptor PTKs  
5 or nontransmembrane, nonreceptor PTK proteins. Transmembrane tyrosine kinases function as  
receptors for most growth factors. Growth factors bind to the receptor tyrosine kinase (RTK),  
which causes the receptor to phosphorylate itself (autophosphorylation) and specific intracellular  
second messenger proteins. Growth factors (GF) that associate with receptor PTKs include  
epidermal GF, platelet-derived GF, fibroblast GF, hepatocyte GF, insulin and insulin-like GFs,  
10 nerve GF, vascular endothelial GF, and macrophage colony stimulating factor.

Nontransmembrane, nonreceptor PTKs lack transmembrane regions and, instead, form  
signaling complexes with the cytosolic domains of plasma membrane receptors. Receptors that  
function through non-receptor PTKs include those for cytokines and hormones (growth hormone  
and prolactin), and antigen-specific receptors on T and B lymphocytes.

15 Many PTKs were first identified as oncogene products in cancer cells in which PTK  
activation was no longer subject to normal cellular controls. In fact, about one third of the known  
oncogenes encode PTKs. Furthermore, cellular transformation (oncogenesis) is often accompanied  
by increased tyrosine phosphorylation activity (Charbonneau, H. and N.K. Tonks (1992) Annu. Rev.  
Cell Biol. 8:463-493). Regulation of PTK activity may therefore be an important strategy in  
20 controlling some types of cancer.

### Protein Serine/Threonine Kinases

Protein serine/threonine kinases (STKs) are nontransmembrane proteins. A subclass of  
STKs are known as ERKs (extracellular signal regulated kinases) or MAPs (mitogen-activated  
protein kinases) and are activated after cell stimulation by a variety of hormones and growth factors.  
25 Cell stimulation induces a signaling cascade leading to phosphorylation of MEK (MAP/ERK  
kinase) which, in turn, activates ERK via serine and threonine phosphorylation. A varied number of  
proteins represent the downstream effectors for the active ERK and implicate it in the control of cell  
proliferation and differentiation, as well as regulation of the cytoskeleton. Activation of ERK is  
normally transient, and cells possess dual specificity phosphatases that are responsible for its down-  
30 regulation. Also, numerous studies have shown that elevated ERK activity is associated with some  
cancers. Other STKs include the second messenger dependent protein kinases such as the  
cyclic-AMP dependent protein kinases (PKA), calcium-calmodulin (CaM) dependent protein  
kinases, and the mitogen-activated protein kinases (MAP); the cyclin-dependent protein kinases;  
checkpoint and cell cycle kinases; Numb-associated kinase (Nak); human Fused (hFu);  
35 proliferation-related kinases; 5'-AMP-activated protein kinases; and kinases involved in apoptosis.



One member of the ERK family of MAP kinases, ERK 7, is a novel 61-kDa protein that has motif similarities to ERK1 and ERK2, but is not activated by extracellular stimuli as are ERK1 and ERK2 nor by the common activators, c-Jun N-terminal kinase (JNK) and p38 kinase. ERK7 regulates its nuclear localization and inhibition of growth through its C-terminal tail, not through the kinase domain as is typical with other MAP kinases (Abe, M.K. (1999) Mol. Cell. Biol. 19:1301-1312).

- The second messenger dependent protein kinases primarily mediate the effects of second messengers such as cyclic AMP (cAMP), cyclic GMP, inositol triphosphate, phosphatidylinositol, 3,4,5-triphosphate, cyclic ADP ribose, arachidonic acid, diacylglycerol and calcium-calmodulin.
- 10 The PKAs are involved in mediating hormone-induced cellular responses and are activated by cAMP produced within the cell in response to hormone stimulation. cAMP is an intracellular mediator of hormone action in all animal cells that have been studied. Hormone-induced cellular responses include thyroid hormone secretion, cortisol secretion, progesterone secretion, glycogen breakdown, bone resorption, and regulation of heart rate and force of heart muscle contraction.
- 15 PKA is found in all animal cells and is thought to account for the effects of cAMP in most of these cells. Altered PKA expression is implicated in a variety of disorders and diseases including cancer, thyroid disorders, diabetes, atherosclerosis, and cardiovascular disease (Isselbacher, K.J. et al. (1994) Harrison's Principles of Internal Medicine, McGraw-Hill, New York NY, pp. 416-431, 1887).
- 20 The casein kinase I (CKI) gene family is another subfamily of serine/threonine protein kinases. This continuously expanding group of kinases have been implicated in the regulation of numerous cytoplasmic and nuclear processes, including cell metabolism and DNA replication and repair. CKI enzymes are present in the membranes, nucleus, cytoplasm and cytoskeleton of eukaryotic cells, and on the mitotic spindles of mammalian cells (Fish, K.J. et al. (1995) J. Biol. Chem. 270:14875-14883).

The CKI family members all have a short amino-terminal domain of 9-76 amino acids, a highly conserved kinase domain of 284 amino acids, and a variable carboxyl-terminal domain that ranges from 24 to over 200 amino acids in length (Cegielska, A. et al. (1998) J. Biol. Chem. 273:1357-1364). The CKI family is comprised of highly related proteins, as seen by the

30 identification of isoforms of casein kinase I from a variety of sources. There are at least five mammalian isoforms,  $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ , and  $\epsilon$ . Fish et al. identified CKI-epsilon from a human placenta cDNA library. It is a basic protein of 416 amino acids and is closest to CKI-delta. Through recombinant expression, it was determined to phosphorylate known CKI substrates and was inhibited by the CKI-specific inhibitor CKI-7. The human gene for CKI-epsilon was able to rescue

35 yeast with a slow-growth phenotype caused by deletion of the yeast CKI locus, HRR250 (Fish et al.,

supra).

The mammalian circadian mutation tau was found to be a semidominant autosomal allele of CKI-epsilon that markedly shortens period length of circadian rhythms in Syrian hamsters. The tau locus is encoded by casein kinase I-epsilon, which is also a homolog of the *Drosophila* circadian gene double-time. Studies of both the wildtype and tau mutant CKI-epsilon enzyme indicated that the mutant enzyme has a noticeable reduction in the maximum velocity and autophosphorylation state. Further, *in vitro*, CKI-epsilon is able to interact with mammalian PERIOD proteins, while the mutant enzyme is deficient in its ability to phosphorylate PERIOD. Lowrey et al. have proposed that CKI-epsilon plays a major role in delaying the negative feedback signal within the transcription-translation-based autoregulatory loop that composes the core of the circadian mechanism. Therefore the CKI-epsilon enzyme is an ideal target for pharmaceutical compounds influencing circadian rhythms, jet-lag and sleep, in addition to other physiologic and metabolic processes under circadian regulation (Lowrey, P.L. et al. (2000) Science 288:483-491).

#### Calcium-Calmodulin Dependent Protein Kinases

Calcium-calmodulin dependent (CaM) kinases are involved in regulation of smooth muscle contraction, glycogen breakdown (phosphorylase kinase), and neurotransmission (CaM kinase I and CaM kinase II). CaM dependent protein kinases are activated by calmodulin, an intracellular calcium receptor, in response to the concentration of free calcium in the cell. Many CaM kinases are also activated by phosphorylation. Some CaM kinases are also activated by autophosphorylation or by other regulatory kinases. CaM kinase I phosphorylates a variety of substrates including the neurotransmitter-related proteins synapsin I and II, the gene transcription regulator, CREB, and the cystic fibrosis conductance regulator protein, CFTR (Haribabu, B. et al. (1995) EMBO J. 14:3679-3686). CaM kinase II also phosphorylates synapsin at different sites and controls the synthesis of catecholamines in the brain through phosphorylation and activation of tyrosine hydroxylase. CaM kinase II controls the synthesis of catecholamines and serotonin, through phosphorylation/activation of tyrosine hydroxylase and tryptophan hydroxylase, respectively (Fujisawa, H. (1990) BioEssays 12:27-29). The mRNA encoding a calmodulin-binding protein kinase-like protein was found to be enriched in mammalian forebrain. This protein is associated with vesicles in both axons and dendrites and accumulates largely postnatally. The amino acid sequence of this protein is similar to CaM-dependent STKs, and the protein binds calmodulin in the presence of calcium (Godbout, M. et al. (1994) J. Neurosci. 14:1-13).

Homeodomain-interacting protein kinases (HIPKs) are serine/threonine kinases and novel members of the DYRK kinase subfamily (Hofmann, T.G. et al. (2000) Biochimie 82:1123-1127). HIPKs contain a conserved protein kinase domain separated from a domain that interacts with homeoproteins. HIPKs are nuclear kinases, and HIPK2 is highly expressed in neuronal tissue (Kim,

- Y.H. et al. (1998) *J. Biol. Chem.* 273:25875-25879; Wang, Y. et al. (2001) *Biochim. Biophys. Acta* 1518:168-172). HIPKs act as corepressors for homeodomain transcription factors. This corepressor activity is seen in posttranslational modifications such as ubiquitination and phosphorylation, each of which are important in the regulation of cellular protein function (Kim, Y.H. et al. (1999) *Proc. Natl. Acad. Sci. USA* 96:12350-12355).

The human h-warts protein, a homolog of *Drosophila* warts tumor suppressor gene, maps to chromosome 6q24-25.1. It has a serine/threonine kinase domain and is localized to centrosomes in interphase cells. It is involved in mitosis and functions as a component of the mitotic apparatus (Nishiyama, Y. et al. (1999) *FEBS Lett.* 459:159-165).

#### 10 Calcium-Calmodulin Dependent Protein Kinases

- Calcium-calmodulin dependent (CaM) kinases are involved in regulation of smooth muscle contraction, glycogen breakdown (phosphorylase kinase), and neurotransmission (CaM kinase I and CaM kinase II). CaM dependent protein kinases are activated by calmodulin, an intracellular calcium receptor, in response to the concentration of free calcium in the cell. Many CaM kinases are also activated by phosphorylation. Some CaM kinases are also activated by autophosphorylation or by other regulatory kinases. CaM kinase I phosphorylates a variety of substrates including the neurotransmitter-related proteins synapsin I and II, the gene transcription regulator, CREB, and the cystic fibrosis conductance regulator protein, CFTR (Haribabu, B. et al. (1995) *EMBO J.* 14:3679-3686). CaM kinase II also phosphorylates synapsin at different sites and controls the synthesis of catecholamines in the brain through phosphorylation and activation of tyrosine hydroxylase. CaM kinase II controls the synthesis of catecholamines and serotonin, through phosphorylation/activation of tyrosine hydroxylase and tryptophan hydroxylase, respectively (Fujisawa, H. (1990) *BioEssays* 12:27-29). The mRNA encoding a calmodulin-binding protein kinase-like protein was found to be enriched in mammalian forebrain. This protein is associated with vesicles in both axons and dendrites and accumulates largely postnatally. The amino acid sequence of this protein is similar to CaM-dependent STKs, and the protein binds calmodulin in the presence of calcium (Godbout, M. et al. (1994) *J. Neurosci.* 14:1-13).

#### Mitogen-Activated Protein Kinases

- The mitogen-activated protein kinases (MAP), which mediate signal transduction from the cell surface to the nucleus via phosphorylation cascades, are another STK family that regulates intracellular signaling pathways. Several subgroups have been identified, and each manifests different substrate specificities and responds to distinct extracellular stimuli (Egan, S.E. and R.A. Weinberg (1993) *Nature* 365:781-783). There are three kinase modules comprising the MAP kinase cascade: MAPK (MAP), MAPK kinase (MAP2K, MAPKK, or MKK), and MKK kinase (MAP3K, MAPKKK, OR MEKK) (Wang, X.S. et al (1998) *Biochem. Biophys. Res. Commun.* 253:33-37).

The extracellular-regulated kinase (ERK) pathway is activated by growth factors and mitogens, for example, epidermal growth factor (EGF), ultraviolet light, hyperosmolar medium, heat shock, or endotoxic lipopolysaccharide (LPS). The closely related though distinct parallel pathways, the c-Jun N-terminal kinase (JNK), or stress-activated kinase (SAPK) pathway, and the p38 kinase  
5 pathway are activated by stress stimuli and proinflammatory cytokines such as tumor necrosis factor (TNF) and interleukin-1 (IL-1). Altered MAP kinase expression is implicated in a variety of disease conditions including cancer, inflammation, immune disorders, and disorders affecting growth and development.. MAP kinase signaling pathways are present in mammalian cells as well as in yeast.

The family of p21-activated protein kinases (PAKs) appear to be present in all organisms  
10 that have Cdc42-like GTPases. In mammalian cells, PAKs have been implicated in the activation of mitogen-activated protein kinase cascades. PAK functions also include the dissolution of cytoskeletal stress fibers and reorganization of focal complexes (Manser, E. et al. (1997) Mol. Cell Biol.17(3):1129-1143).

#### **Cyclin-Dependent Protein Kinases**

15 The cyclin-dependent protein kinases (CDKs) are STKs that control the progression of cells through the cell cycle. The entry and exit of a cell from mitosis are regulated by the synthesis and destruction of a family of activating proteins called cyclins. Cyclins are small regulatory proteins that bind to and activate CDKs, which then phosphorylate and activate selected proteins involved in the mitotic process. CDKs are unique in that they require multiple inputs to become activated. In  
20 addition to cyclin binding, CDK activation requires the phosphorylation of a specific threonine residue and the dephosphorylation of a specific tyrosine residue on the CDK.

Another family of STKs associated with the cell cycle are the NIMA (never in mitosis)-related kinases (Neks). Both CDKs and Neks are involved in duplication, maturation, and separation of the microtubule organizing center, the centrosome, in animal cells (Fry, A.M. et al.  
25 (1998) EMBO J. 17:470-481).

#### **Checkpoint and Cell Cycle Kinases**

In the process of cell division, the order and timing of cell cycle transitions are under control of cell cycle checkpoints, which ensure that critical events such as DNA replication and chromosome segregation are carried out with precision. If DNA is damaged, e.g. by radiation, a  
30 checkpoint pathway is activated that arrests the cell cycle to provide time for repair. If the damage is extensive, apoptosis is induced. In the absence of such checkpoints, the damaged DNA is inherited by aberrant cells which may cause proliferative disorders such as cancer. Protein kinases play an important role in this process. For example, a specific kinase, checkpoint kinase 1 (Chk1), has been identified in yeast and mammals, and is activated by DNA damage in yeast. Activation of  
35 Chk1 leads to the arrest of the cell at the G2/M transition (Sanchez, Y. et al. (1997) Science

277:1497-1501). Specifically, Chk1 phosphorylates the cell division cycle phosphatase CDC25, inhibiting its normal function which is to dephosphorylate and activate the cyclin-dependent kinase Cdc2. Cdc2 activation controls the entry of cells into mitosis (Peng, C.-Y. et al. (1997) Science 277:1501-1505). Thus, activation of Chk1 prevents the damaged cell from entering mitosis. A  
 5 deficiency in a checkpoint kinase, such as Chk1, may also contribute to cancer by failure to arrest cells with damaged DNA at other checkpoints such as G2/M.

#### **Proliferation-Related Kinases**

Proliferation-related kinase is a serum/cytokine inducible STK that is involved in regulation of the cell cycle and cell proliferation in human megakaryocytic cells (Li, B. et al. (1996) J. Biol.  
 10 Chem. 271:19402-19408). Proliferation-related kinase is related to the polo (derived from Drosophila polo gene) family of STKs implicated in cell division. Proliferation-related kinase is downregulated in lung tumor tissue and may be a proto-oncogene whose deregulated expression in normal tissue leads to oncogenic transformation.

#### **5'-AMP-activated protein kinase**

15 A ligand-activated STK protein kinase is 5'-AMP-activated protein kinase (AMPK) (Gao, G. et al. (1996) J. Biol Chem. 271:8675-8681). Mammalian AMPK is a regulator of fatty acid and sterol synthesis through phosphorylation of the enzymes acetyl-CoA carboxylase and hydroxymethylglutaryl-CoA reductase and mediates responses of these pathways to cellular stresses such as heat shock and depletion of glucose and ATP. AMPK is a heterotrimeric complex  
 20 comprised of a catalytic alpha subunit and two non-catalytic beta and gamma subunits that are believed to regulate the activity of the alpha subunit. Subunits of AMPK have a much wider distribution in non-lipogenic tissues such as brain, heart, spleen, and lung than expected. This distribution suggests that its role may extend beyond regulation of lipid metabolism alone.

The RET (rearranged during transfection) proto-oncogene encodes a tyrosine kinase  
 25 receptor involved in both multiple endocrine neoplasia type 2, an inherited cancer syndrome, and Hirschsprung disease, a developmental defect of enteric neurons. RET and its functional ligand, glial cell line-derived neurotrophic factor, play key roles in the development of the human enteric nervous system (Pachnis, V. et al. (1998) Am. J. Physiol. 275:G183-G186).

#### **Kinases in Apoptosis**

30 Apoptosis is a highly regulated signaling pathway leading to cell death that plays a crucial role in tissue development and homeostasis. Deregulation of this process is associated with the pathogenesis of a number of diseases including autoimmune diseases, neurodegenerative disorders, and cancer. Various STKs play key roles in this process. ZIP kinase is an STK containing a C-terminal leucine zipper domain in addition to its N-terminal protein kinase domain. This  
 35 C-terminal domain appears to mediate homodimerization and activation of the kinase as well as

interactions with transcription factors such as activating transcription factor, ATF4, a member of the cyclic-AMP responsive element binding protein (ATF/CREB) family of transcriptional factors (Sanjo, H. et al. (1998) J. Biol. Chem. 273:29066-29071). DRAK1 and DRAK2 are STKs that share homology with the death-associated protein kinases (DAP kinases), known to function in  
5 interferon- $\gamma$  induced apoptosis (Sanjo et al., supra). Like ZIP kinase, DAP kinases contain a C-terminal protein-protein interaction domain, in the form of ankyrin repeats, in addition to the N-terminal kinase domain. ZIP, DAP, and DRAK kinases induce morphological changes associated with apoptosis when transfected into NIH3T3 cells (Sanjo et al., supra). However, deletion of either the N-terminal kinase catalytic domain or the C-terminal domain of these proteins abolishes  
10 apoptosis activity, indicating that in addition to the kinase activity, activity in the C-terminal domain is also necessary for apoptosis, possibly as an interacting domain with a regulator or a specific substrate.

RICK is another STK recently identified as mediating a specific apoptotic pathway involving the death receptor, CD95 (Inohara, N. et al. (1998) J. Biol. Chem. 273:12296-12300).  
15 CD95 is a member of the tumor necrosis factor receptor superfamily and plays a critical role in the regulation and homeostasis of the immune system (Nagata, S. (1997) Cell 88:355-365). The CD95 receptor signaling pathway involves recruitment of various intracellular molecules to a receptor complex following ligand binding. This process includes recruitment of the cysteine protease caspase-8 which, in turn, activates a caspase cascade leading to cell death. RICK is composed of an  
20 N-terminal kinase catalytic domain and a C-terminal "caspase-recruitment" domain that interacts with caspase-like domains, indicating that RICK plays a role in the recruitment of caspase-8. This interpretation is supported by the fact that the expression of RICK in human 293T cells promotes activation of caspase-8 and potentiates the induction of apoptosis by various proteins involved in the CD95 apoptosis pathway (Inohara et al., supra).

#### 25 Mitochondrial Protein Kinases

A novel class of eukaryotic kinases, related by sequence to prokaryotic histidine protein kinases, are the mitochondrial protein kinases (MPKs) which seem to have no sequence similarity with other eukaryotic protein kinases. These protein kinases are located exclusively in the mitochondrial matrix space and may have evolved from genes originally present in respiration-  
30 dependent bacteria which were endocytosed by primitive eukaryotic cells. MPKs are responsible for phosphorylation and inactivation of the branched-chain alpha-ketoacid dehydrogenase and pyruvate dehydrogenase complexes (Harris, R.A. et al. (1995) Adv. Enzyme Regul. 34:147-162). Five MPKs have been identified. Four members correspond to pyruvate dehydrogenase kinase isozymes, regulating the activity of the pyruvate dehydrogenase complex, which is an important  
35 regulatory enzyme at the interface between glycolysis and the citric acid cycle. The fifth member

corresponds to a branched-chain alpha-ketoacid dehydrogenase kinase, important in the regulation of the pathway for the disposal of branched-chain amino acids. (Harris, R.A. et al. (1997) Adv. Enzyme Regul. 37:271-293). Both starvation and the diabetic state are known to result in a great increase in the activity of the pyruvate dehydrogenase kinase in the liver, heart and muscle of the rat. This increase contributes in both disease states to the phosphorylation and inactivation of the pyruvate dehydrogenase complex and conservation of pyruvate and lactate for gluconeogenesis (Harris (1995) supra).

### **KINASES WITH NON-PROTEIN SUBSTRATES**

#### **10 Lipid and Inositol kinases**

Lipid kinases phosphorylate hydroxyl residues on lipid head groups. A family of kinases involved in phosphorylation of phosphatidylinositol (PI) has been described, each member phosphorylating a specific carbon on the inositol ring (Leevers, S.J. et al. (1999) Curr. Opin. Cell Biol. 11:219-225). The phosphorylation of phosphatidylinositol is involved in activation of the protein kinase C signaling pathway. The inositol phospholipids (phosphoinositides) intracellular signaling pathway begins with binding of a signaling molecule to a G-protein linked receptor in the plasma membrane. This leads to the phosphorylation of phosphatidylinositol (PI) residues on the inner side of the plasma membrane by inositol kinases, thus converting PI residues to the biphosphate state (PIP<sub>2</sub>). PIP<sub>2</sub> is then cleaved into inositol triphosphate (IP<sub>3</sub>) and diacylglycerol. These two products act as mediators for separate signaling pathways. Cellular responses that are mediated by these pathways are glycogen breakdown in the liver in response to vasopressin, smooth muscle contraction in response to acetylcholine, and thrombin-induced platelet aggregation.

PI 3-kinase (PI3K), which phosphorylates the D3 position of PI and its derivatives, has a central role in growth factor signal cascades involved in cell growth, differentiation, and metabolism. PI3K is a heterodimer consisting of an adapter subunit and a catalytic subunit. The adapter subunit acts as a scaffolding protein, interacting with specific tyrosine-phosphorylated proteins, lipid moieties, and other cytosolic factors. When the adapter subunit binds tyrosine phosphorylated targets, such as the insulin responsive substrate (IRS)-1, the catalytic subunit is activated and converts PI (4,5) bisphosphate (PIP<sub>2</sub>) to PI (3,4,5) P<sub>3</sub> (PIP<sub>3</sub>). PIP<sub>3</sub> then activates a number of other proteins, including PKA, protein kinase B (PKB), protein kinase C (PKC), glycogen synthase kinase (GSK)-3, and p70 ribosomal s6 kinase. PI3K also interacts directly with the cytoskeletal organizing proteins, Rac, rho, and cdc42 (Shepherd, P.R. et al. (1998) Biochem. J. 333:471-490). Animal models for diabetes, such as *obese* and *fat* mice, have altered PI3K adapter subunit levels. Specific mutations in the adapter subunit have also been found in an insulin-resistant Danish population, suggesting a role for PI3K in type-2 diabetes (Shepard, supra).

An example of lipid kinase phosphorylation activity is the phosphorylation of D-erythro-sphingosine to the sphingolipid metabolite, sphingosine-1-phosphate (SPP). SPP has emerged as a novel lipid second-messenger with both extracellular and intracellular actions (Kohama, T. et al. (1998) *J. Biol. Chem.* 273:23722-23728). Extracellularly, SPP is a ligand for the G-protein coupled receptor EDG-1 (endothelial-derived, G-protein coupled receptor). Intracellularly, SPP regulates cell growth, survival, motility, and cytoskeletal changes. SPP levels are regulated by sphingosine kinases that specifically phosphorylate D-erythro-sphingosine to SPP. The importance of sphingosine kinase in cell signaling is indicated by the fact that various stimuli, including platelet-derived growth factor (PDGF), nerve growth factor, and activation of protein kinase C, increase cellular levels of SPP by activation of sphingosine kinase, and the fact that competitive inhibitors of the enzyme selectively inhibit cell proliferation induced by PDGF (Kohama et al., *supra*).

PKC is also activated by diacylglycerol (DAG). Phorbol esters (PE) are analogs of DAG and tumor promoters that cause a variety of physiological changes when administered to cells and tissues. PE and DAG bind to the N-terminal region of PKC. This region contains one or more copies of a cysteine-rich domain about 50 amino-acid residues long and essential for DAG/PE-binding. Diacylglycerol kinase (DGK), the enzyme that converts DAG into phosphatidate, contains two copies of the DAG/PE-binding domain in its N-terminal section (Azzi, A. et al. (1992) *Eur. J. Biochem.* 208:547-557).

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#### **Purine Nucleotide Kinases**

The purine nucleotide kinases, adenylate kinase (ATP:AMP phosphotransferase, or AdK) and guanylate kinase (ATP:GMP phosphotransferase, or GuK) play a key role in nucleotide metabolism and are crucial to the synthesis and regulation of cellular levels of ATP and GTP,



respectively. These two molecules are precursors in DNA and RNA synthesis in growing cells and provide the primary source of biochemical energy in cells (ATP), and signal transduction pathways (GTP). Inhibition of various steps in the synthesis of these two molecules has been the basis of many antiproliferative drugs for cancer and antiviral therapy (Pillwein, K. et al. (1990) Cancer Res. 50:1576-1579).

AdK is found in almost all cell types and is especially abundant in cells having high rates of ATP synthesis and utilization such as skeletal muscle. In these cells AdK is physically associated with mitochondria and myofibrils, the subcellular structures that are involved in energy production and utilization, respectively. Recent studies have demonstrated a major function for AdK in transferring high energy phosphoryls from metabolic processes generating ATP to cellular components consuming ATP (Zelevnikar, R.J. et al. (1995) J. Biol. Chem. 270:7311-7319). Thus AdK may have a pivotal role in maintaining energy production in cells, particularly those having a high rate of growth or metabolism such as cancer cells, and may provide a target for suppression of its activity in order to treat certain cancers. Alternatively, reduced AdK activity may be a source of various metabolic, muscle-energy disorders that can result in cardiac or respiratory failure and may be treatable by increasing AdK activity.

GuK, in addition to providing a key step in the synthesis of GTP for RNA and DNA synthesis, also fulfills an essential function in signal transduction pathways of cells through the regulation of GDP and GTP. Specifically, GTP binding to membrane associated G proteins mediates the activation of cell receptors, subsequent intracellular activation of adenylyl cyclase, and production of the second messenger, cyclic AMP. GDP binding to G proteins inhibits these processes. GDP and GTP levels also control the activity of certain oncogenic proteins such as p21<sup>ras</sup> known to be involved in control of cell proliferation and oncogenesis (Bos, J.L. (1989) Cancer Res. 49:4682-4689). High ratios of GTP:GDP caused by suppression of GuK cause activation of p21<sup>ras</sup> and promote oncogenesis. Increasing GuK activity to increase levels of GDP and reduce the GTP:GDP ratio may provide a therapeutic strategy to reverse oncogenesis.

GuK is an important enzyme in the phosphorylation and activation of certain antiviral drugs useful in the treatment of herpes virus infections. These drugs include the guanine homologs acyclovir and bucciclovir (Miller, W.H. and R.L. Miller (1980) J. Biol. Chem. 255:7204-7207; Stenberg, K. et al. (1986) J. Biol. Chem. 261:2134-2139). Increasing GuK activity in infected cells may provide a therapeutic strategy for augmenting the effectiveness of these drugs and possibly for reducing the necessary dosages of the drugs.

#### Pyrimidine Kinases

The pyrimidine kinases are deoxycytidine kinase and thymidine kinase 1 and 2. Deoxycytidine kinase is located in the nucleus, and thymidine kinase 1 and 2 are found in the

cytosol (Johansson, M. et al. (1997) Proc. Natl. Acad. Sci. USA 94:11941-11945). Phosphorylation of deoxyribonucleosides by pyrimidine kinases provides an alternative pathway for de novo synthesis of DNA precursors. The role of pyrimidine kinases, like purine kinases, in phosphorylation is critical to the activation of several chemotherapeutically important nucleoside analogues (Arner E.S. and S. Eriksson (1995) Pharmacol. Ther. 67:155-186).

## **PHOSPHATASES**

Protein phosphatases are generally characterized as either serine/threonine- or tyrosine-specific based on their preferred phospho-amino acid substrate. However, some phosphatases (DSPs, for dual specificity phosphatases) can act on phosphorylated tyrosine, serine, or threonine residues. The protein serine/threonine phosphatases (PSPs) are important regulators of many cAMP-mediated hormone responses in cells. Protein tyrosine phosphatases (PTPs) play a significant role in cell cycle and cell signaling processes. Another family of phosphatases is the acid phosphatase or histidine acid phosphatase (HAP) family whose members hydrolyze phosphate esters at acidic pH conditions.

PSPs are found in the cytosol, nucleus, and mitochondria and in association with cytoskeletal and membranous structures in most tissues, especially the brain. Some PSPs require divalent cations, such as  $\text{Ca}^{2+}$  or  $\text{Mn}^{2+}$ , for activity. PSPs play important roles in glycogen metabolism, muscle contraction, protein synthesis, T cell function, neuronal activity, oocyte maturation, and hepatic metabolism (reviewed in Cohen, P. (1989) Annu. Rev. Biochem. 58:453-508). PSPs can be separated into two classes. The PPP class includes PP1, PP2A, PP2B/calcineurin, PP4, PP5, PP6, and PP7. Members of this class are composed of a homologous catalytic subunit bearing a very highly conserved signature sequence, coupled with one or more regulatory subunits (PROSITE PDOC00115). Further interactions with scaffold and anchoring molecules determine the intracellular localization of PSPs and substrate specificity. The PPM class consists of several closely related isoforms of PP2C and is evolutionarily unrelated to the PPP class.

PP1 dephosphorylates many of the proteins phosphorylated by cyclic AMP-dependent protein kinase (PKA) and is an important regulator of many cAMP-mediated hormone responses in cells. A number of isoforms have been identified, with the alpha and beta forms being produced by alternative splicing of the same gene. Both ubiquitous and tissue-specific targeting proteins for PP1 have been identified. In the brain, inhibition of PP1 activity by the dopamine and adenosine 3',5'-monophosphate-regulated phosphoprotein of 32kDa (DARPP-32) is necessary for normal dopamine response in neostriatal neurons (reviewed in Price, N.E. and M.C. Mumby (1999) Curr. Opin. Neurobiol. 9:336-342). PP1, along with PP2A, has been shown to limit motility in microvascular endothelial cells, suggesting a role for PSPs in the inhibition of angiogenesis (Gabel, S. et al. (1999)

Otolaryngol. Head Neck Surg. 121:463-468).

PP2A is the main serine/threonine phosphatase. The core PP2A enzyme consists of a single 36 kDa catalytic subunit (C) associated with a 65 kDa scaffold subunit (A), whose role is to recruit additional regulatory subunits (B). Three gene families encoding B subunits are known (PR55, 5 PR61, and PR72), each of which contain multiple isoforms, and additional families may exist (Millward, T.A et al. (1999) Trends Biosci. 24:186-191). These "B-type" subunits are cell type- and tissue-specific and determine the substrate specificity, enzymatic activity, and subcellular localization of the holoenzyme. The PR55 family is highly conserved and bears a conserved motif (PROSITE PDOC00785). PR55 increases PP2A activity toward mitogen-activated protein kinase 10 (MAPK) and MAPK kinase (MEK). PP2A dephosphorylates the MAPK active site, inhibiting the cell's entry into mitosis. Several proteins can compete with PR55 for PP2A core enzyme binding, including the CKII kinase catalytic subunit, polyomavirus middle and small T antigens, and SV40 small t antigen. Viruses may use this mechanism to commandeer PP2A and stimulate progression of the cell through the cell cycle (Pallas, D.C. et al. (1992) J. Virol. 66:886-893). Altered MAP 15 kinase expression is also implicated in a variety of disease conditions including cancer, inflammation, immune disorders, and disorders affecting growth and development. PP2A, in fact, can dephosphorylate and modulate the activities of more than 30 protein kinases in vitro, and other evidence suggests that the same is true in vivo for such kinases as PKB, PKC, the calmodulin-dependent kinases, ERK family MAP kinases, cyclin-dependent kinases, and the I $\kappa$ B kinases. 20 (reviewed in Millward et al., supra). PP2A is itself a substrate for CKI and CKII kinases, and can be stimulated by polycationic macromolecules. A PP2A-like phosphatase is necessary to maintain the G1 phase destruction of mammalian cyclins A and B (Bastians, H. et al. (1999) Mol. Biol. Cell 10:3927-3941). PP2A is a major activity in the brain and is implicated in regulating neurofilament stability and normal neural function, particularly the phosphorylation of the microtubule-associated 25 protein tau. Hyperphosphorylation of tau has been proposed to lead to the neuronal degeneration seen in Alzheimer's disease (reviewed in Price and Mumby, supra).

PP2B, or calcineurin, is a Ca<sup>2+</sup>-activated dimeric phosphatase and is particularly abundant in the brain. It consists of catalytic and regulatory subunits, and is activated by the binding of the calcium/calmodulin complex. Calcineurin is the target of the immunosuppressant drugs 30 cyclosporine and FK506. Along with other cellular factors, these drugs interact with calcineurin and inhibit phosphatase activity. In T cells, this blocks the calcium dependent activation of the NF-AT family of transcription factors, leading to immunosuppression. This family is widely distributed, and it is likely that calcineurin regulates gene expression in other tissues as well. In neurons, calcineurin modulates functions which range from the inhibition of neurotransmitter release to 35 desensitization of postsynaptic NMDA-receptor coupled calcium channels to long term memory

(reviewed in Price and Mumby, *supra*).

Other members of the PPP class have recently been identified (Cohen, P.T. (1997) Trends Biochem. Sci. 22:245-251). One of them, PP5, contains regulatory domains with tetratricopeptide repeats. It can be activated by polyunsaturated fatty acids and anionic phospholipids *in vitro* and  
5 appears to be involved in a number of signaling pathways, including those controlled by atrial natriuretic peptide or steroid hormones (reviewed in Andreeva, A.V. and M.A. Kutuzov (1999) Cell Signal. 11:555-562).

PP2C is a ~42kDa monomer with broad substrate specificity and is dependent on divalent cations (mainly  $Mn^{2+}$  or  $Mg^{2+}$ ) for its activity. PP2C proteins share a conserved N-terminal region  
10 with an invariant DGH motif, which contains an aspartate residue involved in cation binding (PROSITE PDOC00792). Targeting proteins and mechanisms regulating PP2C activity have not been identified. PP2C has been shown to inhibit the stress-responsive p38 and Jun kinase (JNK) pathways (Takekawa, M. et al. (1998) EMBO J. 17:4744-4752).

In contrast to PSPs, tyrosine-specific phosphatases (PTPs) are generally monomeric proteins  
15 of very diverse size (from 20kDa to greater than 100kDa) and structure that function primarily in the transduction of signals across the plasma membrane. PTPs are categorized as either soluble phosphatases or transmembrane receptor proteins that contain a phosphatase domain. All PTPs share a conserved catalytic domain of about 300 amino acids which contains the active site. The active site consensus sequence includes a cysteine residue which executes a nucleophilic attack on  
20 the phosphate moiety during catalysis (Neel, B.G. and N.K. Tonks (1997) Curr. Opin. Cell Biol. 9:193-204). Receptor PTPs are made up of an N-terminal extracellular domain of variable length, a transmembrane region, and a cytoplasmic region that generally contains two copies of the catalytic domain. Although only the first copy seems to have enzymatic activity, the second copy apparently affects the substrate specificity of the first. The extracellular domains of some receptor PTPs  
25 contain fibronectin-like repeats, immunoglobulin-like domains, MAM domains (an extracellular motif likely to have an adhesive function), or carbonic anhydrase-like domains (PROSITE PDOC 00323). This wide variety of structural motifs accounts for the diversity in size and specificity of PTPs.

PTPs play important roles in biological processes such as cell adhesion, lymphocyte  
30 activation, and cell proliferation. PTPs  $\mu$  and  $\kappa$  are involved in cell-cell contacts, perhaps regulating cadherin/catenin function. A number of PTPs affect cell spreading, focal adhesions, and cell motility, most of them via the integrin/tyrosine kinase signaling pathway (reviewed in Neel and Tonks, *supra*). CD45 phosphatases regulate signal transduction and lymphocyte activation (Ledbetter, J.A. et al. (1988) Proc. Natl. Acad. Sci. USA 85:8628-8632). Soluble PTPs containing  
35 Src-homology-2 domains have been identified (SHPs), suggesting that these molecules might

interact with receptor tyrosine kinases. SHP-1 regulates cytokine receptor signaling by controlling the Janus family PTKs in hematopoietic cells, as well as signaling by the T-cell receptor and c-Kit (reviewed in Neel and Tonks, *supra*). M-phase inducer phosphatase plays a key role in the induction of mitosis by dephosphorylating and activating the PTK CDC2, leading to cell division

5 (Sadhu, K. et al. (1990) Proc. Natl. Acad. Sci. USA 87:5139-5143). In addition, the genes encoding at least eight PTPs have been mapped to chromosomal regions that are translocated or rearranged in various neoplastic conditions, including lymphoma, small cell lung carcinoma, leukemia, adenocarcinoma, and neuroblastoma (reviewed in Charbonneau, H. and N.K. Tonks (1992) Annu. Rev. Cell Biol. 8:463-493). The PTP enzyme active site comprises the consensus sequence of the

10 MTM1 gene family. The MTM1 gene is responsible for X-linked recessive myotubular myopathy, a congenital muscle disorder that has been linked to Xq28 (Kioschis, P. et al., (1998) Genomics 54:256-266). Many PTKs are encoded by oncogenes, and it is well known that oncogenesis is often accompanied by increased tyrosine phosphorylation activity. It is therefore possible that PTPs may serve to prevent or reverse cell transformation and the growth of various cancers by controlling the

15 levels of tyrosine phosphorylation in cells. This is supported by studies showing that overexpression of PTP can suppress transformation in cells and that specific inhibition of PTP can enhance cell transformation (Charbonneau and Tonks, *supra*).

Dual specificity phosphatases (DSPs) are structurally more similar to the PTPs than the PSPs. DSPs bear an extended PTP active site motif with an additional 7 amino acid residues. DSPs

20 are primarily associated with cell proliferation and include the cell cycle regulators cdc25A, B, and C. The phosphatases DUSP1 and DUSP2 inactivate the MAPK family members ERK (extracellular signal-regulated kinase), JNK (c-Jun N-terminal kinase), and p38 on both tyrosine and threonine residues (PROSITE PDOC 00323, *supra*). In the activated state, these kinases have been implicated in neuronal differentiation, proliferation, oncogenic transformation, platelet aggregation, and

25 apoptosis. Thus, DSPs are necessary for proper regulation of these processes (Muda, M. et al. (1996) J. Biol. Chem. 271:27205-27208). The tumor suppressor PTEN is a DSP that also shows lipid phosphatase activity. It seems to negatively regulate interactions with the extracellular matrix and maintains sensitivity to apoptosis. PTEN has been implicated in the prevention of angiogenesis (Giri, D. and M. Ittmann (1999) Hum. Pathol. 30:419-424) and abnormalities in its expression are

30 associated with numerous cancers (reviewed in Tamura, M. et al. (1999) J. Natl. Cancer Inst. 91:1820-1828).

Histidine acid phosphatase (HAP; EXPASY EC 3.1.3.2), also known as acid phosphatase, hydrolyzes a wide spectrum of substrates including alkyl, aryl, and acyl orthophosphate monoesters and phosphorylated proteins at low pH. HAPs share two regions of conserved sequences, each

35 centered around a histidine residue which is involved in catalytic activity. Members of the HAP

family include lysosomal acid phosphatase (LAP) and prostatic acid phosphatase (PAP), both sensitive to inhibition by L-tartrate (PROSITE PDOC00538).

LAP, an orthophosphoric monoester of the endosomal/lysosomal compartment is a housekeeping gene whose enzymatic activity has been detected in all tissues examined (Geier, C. et al. (1989) *Eur. J. Biochem.* 183:611-616). LAP-deficient mice have progressive skeletal disorder and an increased disposition toward generalized seizures (Saftig, P. et al. (1997) *J. Biol. Chem.* 272:18628-18635). LAP-deficient patients were found to have the following clinical features: intermittent vomiting, hypotonia, lethargy, opisthotonos, terminal bleeding, seizures, and death in early infancy (Online Mendelian Inheritance in Man (OMIM) \*200950).

PAP, a prostate epithelium-specific differentiation antigen produced by the prostate gland, has been used to diagnose and stage prostate cancer. In prostate carcinomas, the enzymatic activity of PAP was shown to be decreased compared with normal or benign prostate hypertrophy cells (Foti, A. G. et al. (1977) *Cancer Res.* 37: 4120-4124). Two forms of PAP have been identified, secreted and intracellular. Mature secreted PAP is detected in the seminal fluid and is active as a glycosylated homodimer with a molecular weight of approximately 100-kilodalton. Intracellular PAP is found to exhibit endogenous phosphotyrosyl protein phosphatase activity and is involved in regulating prostate cell growth (Meng, T.C. and Lin, M.F. (1998) *J. Biol. Chem.* 34: 22096-22104).

Synaptojanin, a polyphosphoinositide phosphatase, dephosphorylates phosphoinositides at positions 3, 4 and 5 of the inositol ring. Synaptojanin is a major presynaptic protein found at clathrin-coated endocytic intermediates in nerve terminals, and binds the clathrin coat-associated protein, EPS15. This binding is mediated by the C-terminal region of synaptojanin-170, which has 3 Asp-Pro-Phe amino acid repeats. Further, this 3 residue repeat had been found to be the binding site for the EH domains of EPS15 (Haffner, C. et al. (1997) *FEBS Lett.* 419:175-180). Additionally, synaptojanin may potentially regulate interactions of endocytic proteins with the plasma membrane, and be involved in synaptic vesicle recycling (Brodin, L. et al. (2000) *Curr. Opin. Neurobiol.* 10:312-320). Studies in mice with a targeted disruption in the synaptojanin 1 gene (*Synj1*) were shown to support coat formation of endocytic vesicles more effectively than was seen in wild-type mice, suggesting that *Synj1* can act as a negative regulator of membrane-coat protein interactions. These findings provide genetic evidence for a crucial role of phosphoinositide metabolism in synaptic vesicle recycling (Cremona, O. et al. (1999) *Cell* 99:179-188).

The discovery of new kinases and phosphatases, and the polynucleotides encoding them, satisfies a need in the art by providing new compositions which are useful in the diagnosis, prevention, and treatment of cardiovascular diseases, immune system disorders, neurological disorders, disorders affecting growth and development, lipid disorders, cell proliferative disorders, and cancers, and in the assessment of the effects of exogenous compounds on the expression of

nucleic acid and amino acid sequences of kinases and phosphatases.

### SUMMARY OF THE INVENTION

The invention features purified polypeptides, kinases and phosphatases, referred to 5 collectively as "KAP" and individually as "KAP-1," "KAP-2," "KAP-3," "KAP-4," "KAP-5," "KAP-6," "KAP-7," "KAP-8," "KAP-9," "KAP-10," "KAP-11," "KAP-12," "KAP-13," "KAP-14," "KAP-15," "KAP-16," "KAP-17," "KAP-18," "KAP-19," and "KAP-20." In one aspect, the invention provides an isolated polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-20, b) a 10 polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-20, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-20, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-20. In one alternative, the invention provides 15 an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:1-20.

The invention further provides an isolated polynucleotide encoding a polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-20, b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of 20 SEQ ID NO:1-20, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-20, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-20. In one alternative, the polynucleotide encodes a polypeptide selected from the group consisting of SEQ ID NO:1-20. In another alternative, the polynucleotide is selected from the group consisting of 25 SEQ ID NO:21-40.

Additionally, the invention provides a recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide encoding a polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-20, b) a polypeptide comprising a naturally occurring amino acid 30 sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-20, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-20, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-20. In one alternative, the invention provides a cell transformed with the recombinant polynucleotide. 35 In another alternative, the invention provides a transgenic organism comprising the recombinant

polynucleotide.

The invention also provides a method for producing a polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-20, b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-20, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-20, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-20. The method comprises a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide encoding the polypeptide, and b) recovering the polypeptide so expressed.

Additionally, the invention provides an isolated antibody which specifically binds to a polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-20, b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-20, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-20, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-20.

The invention further provides an isolated polynucleotide selected from the group consisting of a) a polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:21-40, b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:21-40, c) a polynucleotide complementary to the polynucleotide of a), d) a polynucleotide complementary to the polynucleotide of b), and e) an RNA equivalent of a)-d). In one alternative, the polynucleotide comprises at least 60 contiguous nucleotides.

Additionally, the invention provides a method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide selected from the group consisting of a) a polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:21-40, b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:21-40, c) a polynucleotide complementary to the polynucleotide of a), d) a polynucleotide complementary to the polynucleotide of b), and e) an RNA equivalent of a)-d). The method comprises a) hybridizing the sample with a probe comprising at least 20 contiguous



nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide or fragments thereof, and b) detecting the presence or absence of said hybridization complex, and optionally, if present, the amount thereof. In one alternative, the probe comprises at least 60 contiguous nucleotides.

The invention further provides a method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide selected from the group consisting of a) a polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:21-40, b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:21-40, c) a polynucleotide complementary to the polynucleotide of a), d) a polynucleotide complementary to the polynucleotide of b), and e) an RNA equivalent of a)-d). The method comprises a) amplifying said target polynucleotide or fragment thereof using polymerase chain reaction amplification, and b) detecting the presence or absence of said amplified target polynucleotide or fragment thereof, and, optionally, if present, the amount thereof.

The invention further provides a composition comprising an effective amount of a polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-20, b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-20, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-20, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-20, and a pharmaceutically acceptable excipient. In one embodiment, the composition comprises an amino acid sequence selected from the group consisting of SEQ ID NO:1-20. The invention additionally provides a method of treating a disease or condition associated with decreased expression of functional KAP, comprising administering to a patient in need of such treatment the composition.

The invention also provides a method for screening a compound for effectiveness as an agonist of a polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-20, b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-20, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-20, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group

consisting of SEQ ID NO:1-20. The method comprises a) exposing a sample comprising the polypeptide to a compound, and b) detecting agonist activity in the sample. In one alternative, the invention provides a composition comprising an agonist compound identified by the method and a pharmaceutically acceptable excipient. In another alternative, the invention provides a method of  
5 treating a disease or condition associated with decreased expression of functional KAP, comprising administering to a patient in need of such treatment the composition.

Additionally, the invention provides a method for screening a compound for effectiveness as an antagonist of a polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-20, b) a polypeptide  
10 comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-20, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-20, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-20. The method comprises a) exposing a sample  
15 comprising the polypeptide to a compound, and b) detecting antagonist activity in the sample. In one alternative, the invention provides a composition comprising an antagonist compound identified by the method and a pharmaceutically acceptable excipient. In another alternative, the invention provides a method of treating a disease or condition associated with overexpression of functional KAP, comprising administering to a patient in need of such treatment the composition.

20 The invention further provides a method of screening for a compound that specifically binds to a polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-20, b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-20, c) a biologically active fragment of a polypeptide  
25 having an amino acid sequence selected from the group consisting of SEQ ID NO:1-20, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-20. The method comprises a) combining the polypeptide with at least one test compound under suitable conditions, and b) detecting binding of the polypeptide to the test compound, thereby identifying a compound that specifically binds to the polypeptide.

30 The invention further provides a method of screening for a compound that modulates the activity of a polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-20, b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-20, c) a biologically active fragment of a polypeptide  
35 having an amino acid sequence selected from the group consisting of SEQ ID NO:1-20, and d) an

immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-20. The method comprises a) combining the polypeptide with at least one test compound under conditions permissive for the activity of the polypeptide, b) assessing the activity of the polypeptide in the presence of the test compound, and c) comparing the activity of the polypeptide in the presence of the test compound with the activity of the polypeptide in the absence of the test compound, wherein a change in the activity of the polypeptide in the presence of the test compound is indicative of a compound that modulates the activity of the polypeptide.

The invention further provides a method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a polynucleotide sequence selected from the group consisting of SEQ ID NO:21-40, the method comprising a) exposing a sample comprising the target polynucleotide to a compound, b) detecting altered expression of the target polynucleotide, and c) comparing the expression of the target polynucleotide in the presence of varying amounts of the compound and in the absence of the compound.

The invention further provides a method for assessing toxicity of a test compound, said method comprising a) treating a biological sample containing nucleic acids with the test compound; b) hybridizing the nucleic acids of the treated biological sample with a probe comprising at least 20 contiguous nucleotides of a polynucleotide selected from the group consisting of i) a polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:21-40, ii) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:21-40, iii) a polynucleotide having a sequence complementary to i), iv) a polynucleotide complementary to the polynucleotide of ii), and v) an RNA equivalent of i)-iv). Hybridization occurs under conditions whereby a specific hybridization complex is formed between said probe and a target polynucleotide in the biological sample, said target polynucleotide selected from the group consisting of i) a polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:21-40, ii) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:21-40, iii) a polynucleotide complementary to the polynucleotide of i), iv) a polynucleotide complementary to the polynucleotide of ii), and v) an RNA equivalent of i)-iv). Alternatively, the target polynucleotide comprises a fragment of a polynucleotide sequence selected from the group consisting of i)-v) above; c) quantifying the amount of hybridization complex; and d) comparing the amount of hybridization complex in the treated biological sample with the amount of hybridization complex in an untreated biological sample, wherein a difference in the amount of hybridization complex in the treated biological sample is indicative of toxicity of the test compound.

### BRIEF DESCRIPTION OF THE TABLES

Table 1 summarizes the nomenclature for the full length polynucleotide and polypeptide sequences of the present invention.

5        Table 2 shows the GenBank identification number and annotation of the nearest GenBank homolog for polypeptides of the invention. The probability scores for the matches between each polypeptide and its homolog(s) are also shown.

Table 3 shows structural features of polypeptide sequences of the invention, including predicted motifs and domains, along with the methods, algorithms, and searchable databases used  
10 for analysis of the polypeptides.

Table 4 lists the cDNA and/or genomic DNA fragments which were used to assemble polynucleotide sequences of the invention, along with selected fragments of the polynucleotide sequences.

Table 5 shows the representative cDNA library for polynucleotides of the invention.

15        Table 6 provides an appendix which describes the tissues and vectors used for construction of the cDNA libraries shown in Table 5.

Table 7 shows the tools, programs, and algorithms used to analyze the polynucleotides and polypeptides of the invention, along with applicable descriptions, references, and threshold parameters.

20

### DESCRIPTION OF THE INVENTION

Before the present proteins, nucleotide sequences, and methods are described, it is understood that this invention is not limited to the particular machines, materials and methods described, as these may vary. It is also to be understood that the terminology used herein is for the  
25 purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, a reference to "a host cell" includes a plurality of such host cells, and a reference to "an  
30 antibody" is a reference to one or more antibodies and equivalents thereof known to those skilled in the art, and so forth.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any machines, materials, and methods similar or equivalent to those described  
35 herein can be used to practice or test the present invention, the preferred machines, materials and

methods are now described. All publications mentioned herein are cited for the purpose of describing and disclosing the cell lines, protocols, reagents and vectors which are reported in the publications and which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of 5 prior invention.

## DEFINITIONS

"KAP" refers to the amino acid sequences of substantially purified KAP obtained from any species, particularly a mammalian species, including bovine, ovine, porcine, murine, equine, and human, and from any source, whether natural, synthetic, semi-synthetic, or recombinant.

10 The term "agonist" refers to a molecule which intensifies or mimics the biological activity of KAP. Agonists may include proteins, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of KAP either by directly interacting with KAP or by acting on components of the biological pathway in which KAP participates.

An "allelic variant" is an alternative form of the gene encoding KAP. Allelic variants may 15 result from at least one mutation in the nucleic acid sequence and may result in altered mRNAs or in polypeptides whose structure or function may or may not be altered. A gene may have none, one, or many allelic variants of its naturally occurring form. Common mutational changes which give rise to allelic variants are generally ascribed to natural deletions, additions, or substitutions of nucleotides. Each of these types of changes may occur alone, or in combination with the others, one 20 or more times in a given sequence.

"Altered" nucleic acid sequences encoding KAP include those sequences with deletions, insertions, or substitutions of different nucleotides, resulting in a polypeptide the same as KAP or a polypeptide with at least one functional characteristic of KAP. Included within this definition are polymorphisms which may or may not be readily detectable using a particular oligonucleotide probe 25 of the polynucleotide encoding KAP, and improper or unexpected hybridization to allelic variants, with a locus other than the normal chromosomal locus for the polynucleotide sequence encoding KAP. The encoded protein may also be "altered," and may contain deletions, insertions, or substitutions of amino acid residues which produce a silent change and result in a functionally equivalent KAP. Deliberate amino acid substitutions may be made on the basis of similarity in 30 polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues, as long as the biological or immunological activity of KAP is retained. For example, negatively charged amino acids may include aspartic acid and glutamic acid, and positively charged amino acids may include lysine and arginine. Amino acids with uncharged polar side chains having similar hydrophilicity values may include: asparagine and glutamine; and serine and threonine. 35 Amino acids with uncharged side chains having similar hydrophilicity values may include: leucine,

isoleucine, and valine; glycine and alanine; and phenylalanine and tyrosine.

The terms "amino acid" and "amino acid sequence" refer to an oligopeptide, peptide, polypeptide, or protein sequence, or a fragment of any of these, and to naturally occurring or synthetic molecules. Where "amino acid sequence" is recited to refer to a sequence of a naturally occurring protein molecule, "amino acid sequence" and like terms are not meant to limit the amino acid sequence to the complete native amino acid sequence associated with the recited protein molecule.

"Amplification" relates to the production of additional copies of a nucleic acid sequence. Amplification is generally carried out using polymerase chain reaction (PCR) technologies well known in the art.

The term "antagonist" refers to a molecule which inhibits or attenuates the biological activity of KAP. Antagonists may include proteins such as antibodies, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of KAP either by directly interacting with KAP or by acting on components of the biological pathway in which KAP participates.

The term "antibody" refers to intact immunoglobulin molecules as well as to fragments thereof, such as Fab, F(ab')<sub>2</sub>, and Fv fragments, which are capable of binding an epitopic determinant. Antibodies that bind KAP polypeptides can be prepared using intact polypeptides or using fragments containing small peptides of interest as the immunizing antigen. The polypeptide or oligopeptide used to immunize an animal (e.g., a mouse, a rat, or a rabbit) can be derived from the translation of RNA, or synthesized chemically, and can be conjugated to a carrier protein if desired. Commonly used carriers that are chemically coupled to peptides include bovine serum albumin, thyroglobulin, and keyhole limpet hemocyanin (KLH). The coupled peptide is then used to immunize the animal.

The term "antigenic determinant" refers to that region of a molecule (i.e., an epitope) that makes contact with a particular antibody. When a protein or a fragment of a protein is used to immunize a host animal, numerous regions of the protein may induce the production of antibodies which bind specifically to antigenic determinants (particular regions or three-dimensional structures on the protein). An antigenic determinant may compete with the intact antigen (i.e., the immunogen used to elicit the immune response) for binding to an antibody.

The term "aptamer" refers to a nucleic acid or oligonucleotide molecule that binds to a specific molecular target. Aptamers are derived from an *in vitro* evolutionary process (e.g., SELEX (Systematic Evolution of Ligands by EXponential Enrichment), described in U.S. Patent No. 5,270,163), which selects for target-specific aptamer sequences from large combinatorial libraries. Aptamer compositions may be double-stranded or single-stranded, and may include

deoxyribonucleotides, ribonucleotides, nucleotide derivatives, or other nucleotide-like molecules. The nucleotide components of an aptamer may have modified sugar groups (e.g., the 2'-OH group of a ribonucleotide may be replaced by 2'-F or 2'-NH<sub>2</sub>), which may improve a desired property, e.g., resistance to nucleases or longer lifetime in blood. Aptamers may be conjugated to other molecules, 5 e.g., a high molecular weight carrier to slow clearance of the aptamer from the circulatory system. Aptamers may be specifically cross-linked to their cognate ligands, e.g., by photo-activation of a cross-linker. (See, e.g., Brody, E.N. and L. Gold (2000) J. Biotechnol. 74:5-13.)

The term "intramer" refers to an aptamer which is expressed in vivo. For example, a vaccinia virus-based RNA expression system has been used to express specific RNA aptamers at 10 high levels in the cytoplasm of leukocytes (Blind, M. et al. (1999) Proc. Natl Acad. Sci. USA 96:3606-3610).

The term "spiegelmer" refers to an aptamer which includes L-DNA, L-RNA, or other left-handed nucleotide derivatives or nucleotide-like molecules. Aptamers containing left-handed nucleotides are resistant to degradation by naturally occurring enzymes, which normally act on 15 substrates containing right-handed nucleotides.

The term "antisense" refers to any composition capable of base-pairing with the "sense" (coding) strand of a specific nucleic acid sequence. Antisense compositions may include DNA; RNA; peptide nucleic acid (PNA); oligonucleotides having modified backbone linkages such as phosphorothioates, methylphosphonates, or benzylphosphonates; oligonucleotides having modified 20 sugar groups such as 2'-methoxyethyl sugars or 2'-methoxyethoxy sugars; or oligonucleotides having modified bases such as 5-methyl cytosine, 2'-deoxyuracil, or 7-deaza-2'-deoxyguanosine. Antisense molecules may be produced by any method including chemical synthesis or transcription. Once introduced into a cell, the complementary antisense molecule base-pairs with a naturally occurring nucleic acid sequence produced by the cell to form duplexes which block either transcription or 25 translation. The designation "negative" or "minus" can refer to the antisense strand, and the designation "positive" or "plus" can refer to the sense strand of a reference DNA molecule.

The term "biologically active" refers to a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule. Likewise, "immunologically active" or "immunogenic" refers to the capability of the natural, recombinant, or synthetic KAP, or of any 30 oligopeptide thereof, to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies.

"Complementary" describes the relationship between two single-stranded nucleic acid sequences that anneal by base-pairing. For example, 5'-AGT-3' pairs with its complement, 3'-TCA-5'.

35 A "composition comprising a given polynucleotide sequence" and a "composition

comprising a given amino acid sequence" refer broadly to any composition containing the given polynucleotide or amino acid sequence. The composition may comprise a dry formulation or an aqueous solution. Compositions comprising polynucleotide sequences encoding KAP or fragments of KAP may be employed as hybridization probes. The probes may be stored in freeze-dried form 5 and may be associated with a stabilizing agent such as a carbohydrate. In hybridizations, the probe may be deployed in an aqueous solution containing salts (e.g., NaCl), detergents (e.g., sodium dodecyl sulfate; SDS), and other components (e.g., Denhardt's solution, dry milk, salmon sperm DNA, etc.).

"Consensus sequence" refers to a nucleic acid sequence which has been subjected to 10 repeated DNA sequence analysis to resolve uncalled bases, extended using the XL-PCR kit (Applied Biosystems, Foster City CA) in the 5' and/or the 3' direction, and resequenced, or which has been assembled from one or more overlapping cDNA, EST, or genomic DNA fragments using a computer program for fragment assembly, such as the GELVIEW fragment assembly system (GCG, Madison WI) or Phrap (University of Washington, Seattle WA). Some sequences have been both 15 extended and assembled to produce the consensus sequence.

"Conservative amino acid substitutions" are those substitutions that are predicted to least interfere with the properties of the original protein, i.e., the structure and especially the function of the protein is conserved and not significantly changed by such substitutions. The table below shows amino acids which may be substituted for an original amino acid in a protein and which are 20 regarded as conservative amino acid substitutions.

	Original Residue	Conservative Substitution
	Ala	Gly, Ser
	Arg	His, Lys
	Asn	Asp, Gln, His
25	Asp	Asn, Glu
	Cys	Ala, Ser
	Gln	Asn, Glu, His
	Glu	Asp, Gln, His
	Gly	Ala
30	His	Asn, Arg, Gln, Glu
	Ile	Leu, Val
	Leu	Ile, Val
	Lys	Arg, Gln, Glu
	Met	Leu, Ile
35	Phe	His, Met, Leu, Trp, Tyr
	Ser	Cys, Thr
	Thr	Ser, Val
	Trp	Phe, Tyr
	Tyr	His, Phe, Trp
40	Val	Ile, Leu, Thr

Conservative amino acid substitutions generally maintain (a) the structure of the



polypeptide backbone in the area of the substitution, for example, as a beta sheet or alpha helical conformation, (b) the charge or hydrophobicity of the molecule at the site of the substitution, and/or (c) the bulk of the side chain.

A "deletion" refers to a change in the amino acid or nucleotide sequence that results in the  
5 absence of one or more amino acid residues or nucleotides.

The term "derivative" refers to a chemically modified polynucleotide or polypeptide. Chemical modifications of a polynucleotide can include, for example, replacement of hydrogen by an alkyl, acyl, hydroxyl, or amino group. A derivative polynucleotide encodes a polypeptide which retains at least one biological or immunological function of the natural molecule. A derivative  
10 polypeptide is one modified by glycosylation, pegylation, or any similar process that retains at least one biological or immunological function of the polypeptide from which it was derived.

A "detectable label" refers to a reporter molecule or enzyme that is capable of generating a measurable signal and is covalently or noncovalently joined to a polynucleotide or polypeptide.

"Differential expression" refers to increased or upregulated; or decreased, downregulated,  
15 or absent gene or protein expression, determined by comparing at least two different samples. Such comparisons may be carried out between, for example, a treated and an untreated sample, or a diseased and a normal sample.

"Exon shuffling" refers to the recombination of different coding regions (exons). Since an exon may represent a structural or functional domain of the encoded protein, new proteins may be  
20 assembled through the novel reassortment of stable substructures, thus allowing acceleration of the evolution of new protein functions.

A "fragment" is a unique portion of KAP or the polynucleotide encoding KAP which is identical in sequence to but shorter in length than the parent sequence. A fragment may comprise up to the entire length of the defined sequence, minus one nucleotide/amino acid residue. For  
25 example, a fragment may comprise from 5 to 1000 contiguous nucleotides or amino acid residues. A fragment used as a probe, primer, antigen, therapeutic molecule, or for other purposes, may be at least 5, 10, 15, 16, 20, 25, 30, 40, 50, 60, 75, 100, 150, 250 or at least 500 contiguous nucleotides or amino acid residues in length. Fragments may be preferentially selected from certain regions of a molecule. For example, a polypeptide fragment may comprise a certain length of contiguous amino  
30 acids selected from the first 250 or 500 amino acids (or first 25% or 50%) of a polypeptide as shown in a certain defined sequence. Clearly these lengths are exemplary, and any length that is supported by the specification, including the Sequence Listing, tables, and figures, may be encompassed by the present embodiments.

A fragment of SEQ ID NO:21-40 comprises a region of unique polynucleotide sequence  
35 that specifically identifies SEQ ID NO:21-40, for example, as distinct from any other sequence in

the genome from which the fragment was obtained. A fragment of SEQ ID NO:21-40 is useful, for example, in hybridization and amplification technologies and in analogous methods that distinguish SEQ ID NO:21-40 from related polynucleotide sequences. The precise length of a fragment of SEQ ID NO:21-40 and the region of SEQ ID NO:21-40 to which the fragment corresponds are routinely  
5 determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

A fragment of SEQ ID NO:1-20 is encoded by a fragment of SEQ ID NO:21-40. A fragment of SEQ ID NO:1-20 comprises a region of unique amino acid sequence that specifically identifies SEQ ID NO:1-20. For example, a fragment of SEQ ID NO:1-20 is useful as an immunogenic peptide for the development of antibodies that specifically recognize SEQ ID NO:1-  
10 20. The precise length of a fragment of SEQ ID NO:1-20 and the region of SEQ ID NO:1-20 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

A "full length" polynucleotide sequence is one containing at least a translation initiation codon (e.g., methionine) followed by an open reading frame and a translation termination codon. A  
15 "full length" polynucleotide sequence encodes a "full length" polypeptide sequence.

"Homology" refers to sequence similarity or, interchangeably, sequence identity, between two or more polynucleotide sequences or two or more polypeptide sequences.

The terms "percent identity" and "% identity," as applied to polynucleotide sequences, refer to the percentage of residue matches between at least two polynucleotide sequences aligned using a  
20 standardized algorithm. Such an algorithm may insert, in a standardized and reproducible way, gaps in the sequences being compared in order to optimize alignment between two sequences, and therefore achieve a more meaningful comparison of the two sequences.

Percent identity between polynucleotide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e  
25 sequence alignment program. This program is part of the LASERGENE software package, a suite of molecular biological analysis programs (DNASTAR, Madison WI). CLUSTAL V is described in Higgins, D.G. and P.M. Sharp (1989) CABIOS 5:151-153 and in Higgins, D.G. et al. (1992) CABIOS 8:189-191. For pairwise alignments of polynucleotide sequences, the default parameters are set as follows: Ktuple=2, gap penalty=5, window=4, and "diagonals saved"=4. The "weighted"  
30 residue weight table is selected as the default. Percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polynucleotide sequences.

Alternatively, a suite of commonly used and freely available sequence comparison algorithms is provided by the National Center for Biotechnology Information (NCBI) Basic Local Alignment Search Tool (BLAST) (Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410), which is  
35 available from several sources, including the NCBI, Bethesda, MD, and on the Internet at

<http://www.ncbi.nlm.nih.gov/BLAST/>. The BLAST software suite includes various sequence analysis programs including "blastn," that is used to align a known polynucleotide sequence with other polynucleotide sequences from a variety of databases. Also available is a tool called "BLAST 2 Sequences" that is used for direct pairwise comparison of two nucleotide sequences. "BLAST 2 Sequences" can be accessed and used interactively at <http://www.ncbi.nlm.nih.gov/gorf/bl2.html>. The "BLAST 2 Sequences" tool can be used for both blastn and blastp (discussed below). BLAST programs are commonly used with gap and other parameters set to default settings. For example, to compare two nucleotide sequences, one may use blastn with the "BLAST 2 Sequences" tool Version 2.0.12 (April-21-2000) set at default parameters. Such default parameters may be, for

10 example:

*Matrix: BLOSUM62*

*Reward for match: 1*

*Penalty for mismatch: -2*

*Open Gap: 5 and Extension Gap: 2 penalties*

15 *Gap x drop-off: 50*

*Expect: 10*

*Word Size: 11*

*Filter: on*

Percent identity may be measured over the length of an entire defined sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined sequence, for instance, a fragment of at least 20, at least 30, at least 40, at least 50, at least 70, at least 100, or at least 200 contiguous nucleotides. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in the tables, figures, or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

25 Nucleic acid sequences that do not show a high degree of identity may nevertheless encode similar amino acid sequences due to the degeneracy of the genetic code. It is understood that changes in a nucleic acid sequence can be made using this degeneracy to produce multiple nucleic acid sequences that all encode substantially the same protein.

30 The phrases "percent identity" and "% identity," as applied to polypeptide sequences, refer to the percentage of residue matches between at least two polypeptide sequences aligned using a standardized algorithm. Methods of polypeptide sequence alignment are well-known. Some alignment methods take into account conservative amino acid substitutions. Such conservative substitutions, explained in more detail above, generally preserve the charge and hydrophobicity at the site of substitution, thus preserving the structure (and therefore function) of the polypeptide.

Percent identity between polypeptide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program (described and referenced above). For pairwise alignments of polypeptide sequences using CLUSTAL V, the default parameters are set as follows: Ktuple=1, gap 5 penalty=3, window=5, and "diagonals saved"=5. The PAM250 matrix is selected as the default residue weight table. As with polynucleotide alignments, the percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polypeptide sequence pairs.

Alternatively the NCBI BLAST software suite may be used. For example, for a pairwise comparison of two polypeptide sequences, one may use the "BLAST 2 Sequences" tool Version 10 2.0.12 (April-21-2000) with blastp set at default parameters. Such default parameters may be, for example:

*Matrix: BLOSUM62*

*Open Gap: 11 and Extension Gap: 1 penalties*

*Gap x drop-off: 50*

15 *Expect: 10*

*Word Size: 3*

*Filter: on*

Percent identity may be measured over the length of an entire defined polypeptide sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, 20 for example, over the length of a fragment taken from a larger, defined polypeptide sequence, for instance, a fragment of at least 15, at least 20, at least 30, at least 40, at least 50, at least 70 or at least 150 contiguous residues. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in the tables, figures or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

25 "Human artificial chromosomes" (HACs) are linear microchromosomes which may contain DNA sequences of about 6 kb to 10 Mb in size and which contain all of the elements required for chromosome replication, segregation and maintenance.

The term "humanized antibody" refers to an antibody molecule in which the amino acid sequence in the non-antigen binding regions has been altered so that the antibody more closely 30 resembles a human antibody, and still retains its original binding ability.

"Hybridization" refers to the process by which a polynucleotide strand anneals with a complementary strand through base pairing under defined hybridization conditions. Specific hybridization is an indication that two nucleic acid sequences share a high degree of complementarity. Specific hybridization complexes form under permissive annealing conditions 35 and remain hybridized after the "washing" step(s). The washing step(s) is particularly important in

determining the stringency of the hybridization process, with more stringent conditions allowing less non-specific binding, i.e., binding between pairs of nucleic acid strands that are not perfectly matched. Permissive conditions for annealing of nucleic acid sequences are routinely determinable by one of ordinary skill in the art and may be consistent among hybridization experiments, whereas wash conditions may be varied among experiments to achieve the desired stringency, and therefore hybridization specificity. Permissive annealing conditions occur, for example, at 68°C in the presence of about 6 x SSC, about 1% (w/v) SDS, and about 100 µg/ml sheared, denatured salmon sperm DNA.

Generally, stringency of hybridization is expressed, in part, with reference to the temperature under which the wash step is carried out. Such wash temperatures are typically selected to be about 5°C to 20°C lower than the thermal melting point ( $T_m$ ) for the specific sequence at a defined ionic strength and pH. The  $T_m$  is the temperature (under defined ionic strength and pH) at which 50% of the target sequence hybridizes to a perfectly matched probe. An equation for calculating  $T_m$  and conditions for nucleic acid hybridization are well known and can be found in Sambrook, J. et al. (1989) Molecular Cloning: A Laboratory Manual, 2<sup>nd</sup> ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; specifically see volume 2, chapter 9.

High stringency conditions for hybridization between polynucleotides of the present invention include wash conditions of 68°C in the presence of about 0.2 x SSC and about 0.1% SDS, for 1 hour. Alternatively, temperatures of about 65°C, 60°C, 55°C, or 42°C may be used. SSC concentration may be varied from about 0.1 to 2 x SSC, with SDS being present at about 0.1%. Typically, blocking reagents are used to block non-specific hybridization. Such blocking reagents include, for instance, sheared and denatured salmon sperm DNA at about 100-200 µg/ml. Organic solvent, such as formamide at a concentration of about 35-50% v/v, may also be used under particular circumstances, such as for RNA:DNA hybridizations. Useful variations on these wash conditions will be readily apparent to those of ordinary skill in the art. Hybridization, particularly under high stringency conditions, may be suggestive of evolutionary similarity between the nucleotides. Such similarity is strongly indicative of a similar role for the nucleotides and their encoded polypeptides.

The term "hybridization complex" refers to a complex formed between two nucleic acid sequences by virtue of the formation of hydrogen bonds between complementary bases. A hybridization complex may be formed in solution (e.g.,  $C_0t$  or  $R_0t$  analysis) or formed between one nucleic acid sequence present in solution and another nucleic acid sequence immobilized on a solid support (e.g., paper, membranes, filters, chips, pins or glass slides, or any other appropriate substrate to which cells or their nucleic acids have been fixed).

The words "insertion" and "addition" refer to changes in an amino acid or nucleotide

sequence resulting in the addition of one or more amino acid residues or nucleotides, respectively.

"Immune response" can refer to conditions associated with inflammation, trauma, immune disorders, or infectious or genetic disease, etc. These conditions can be characterized by expression of various factors, e.g., cytokines, chemokines, and other signaling molecules, which may affect cellular and systemic defense systems.

An "immunogenic fragment" is a polypeptide or oligopeptide fragment of KAP which is capable of eliciting an immune response when introduced into a living organism, for example, a mammal. The term "immunogenic fragment" also includes any polypeptide or oligopeptide fragment of KAP which is useful in any of the antibody production methods disclosed herein or known in the art.

The term "microarray" refers to an arrangement of a plurality of polynucleotides, polypeptides, or other chemical compounds on a substrate.

The terms "element" and "array element" refer to a polynucleotide, polypeptide, or other chemical compound having a unique and defined position on a microarray.

The term "modulate" refers to a change in the activity of KAP. For example, modulation may cause an increase or a decrease in protein activity, binding characteristics, or any other biological, functional, or immunological properties of KAP.

The phrases "nucleic acid" and "nucleic acid sequence" refer to a nucleotide, oligonucleotide, polynucleotide, or any fragment thereof. These phrases also refer to DNA or RNA of genomic or synthetic origin which may be single-stranded or double-stranded and may represent the sense or the antisense strand, to peptide nucleic acid (PNA), or to any DNA-like or RNA-like material.

"Operably linked" refers to the situation in which a first nucleic acid sequence is placed in a functional relationship with a second nucleic acid sequence. For instance, a promoter is operably linked to a coding sequence if the promoter affects the transcription or expression of the coding sequence. Operably linked DNA sequences may be in close proximity or contiguous and, where necessary to join two protein coding regions, in the same reading frame.

"Peptide nucleic acid" (PNA) refers to an antisense molecule or anti-gene agent which comprises an oligonucleotide of at least about 5 nucleotides in length linked to a peptide backbone of amino acid residues ending in lysine. The terminal lysine confers solubility to the composition. PNAs preferentially bind complementary single stranded DNA or RNA and stop transcript elongation, and may be pegylated to extend their lifespan in the cell.

"Post-translational modification" of an KAP may involve lipidation, glycosylation, phosphorylation, acetylation, racemization, proteolytic cleavage, and other modifications known in the art. These processes may occur synthetically or biochemically. Biochemical modifications will

vary by cell type depending on the enzymatic milieu of KAP.

"Probe" refers to nucleic acid sequences encoding KAP, their complements, or fragments thereof, which are used to detect identical, allelic or related nucleic acid sequences. Probes are isolated oligonucleotides or polynucleotides attached to a detectable label or reporter molecule.

5 Typical labels include radioactive isotopes, ligands, chemiluminescent agents, and enzymes.

"Primers" are short nucleic acids, usually DNA oligonucleotides, which may be annealed to a target polynucleotide by complementary base-pairing. The primer may then be extended along the target DNA strand by a DNA polymerase enzyme. Primer pairs can be used for amplification (and identification) of a nucleic acid sequence, e.g., by the polymerase chain reaction (PCR).

10 Probes and primers as used in the present invention typically comprise at least 15 contiguous nucleotides of a known sequence. In order to enhance specificity, longer probes and primers may also be employed, such as probes and primers that comprise at least 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, or at least 150 consecutive nucleotides of the disclosed nucleic acid sequences. Probes and primers may be considerably longer than these examples, and it is understood that any  
15 length supported by the specification, including the tables, figures, and Sequence Listing, may be used.

Methods for preparing and using probes and primers are described in the references, for example Sambrook, J. et al. (1989) Molecular Cloning: A Laboratory Manual, 2<sup>nd</sup> ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; Ausubel, F.M. et al. (1987) Current Protocols in Molecular  
20 Biology, Greene Publ. Assoc. & Wiley-Intersciences, New York NY; Innis, M. et al. (1990) PCR Protocols, A Guide to Methods and Applications, Academic Press, San Diego CA. PCR primer pairs can be derived from a known sequence, for example, by using computer programs intended for that purpose such as Primer (Version 0.5, 1991, Whitehead Institute for Biomedical Research, Cambridge MA).

25 Oligonucleotides for use as primers are selected using software known in the art for such purpose. For example, OLIGO 4.06 software is useful for the selection of PCR primer pairs of up to 100 nucleotides each, and for the analysis of oligonucleotides and larger polynucleotides of up to 5,000 nucleotides from an input polynucleotide sequence of up to 32 kilobases. Similar primer selection programs have incorporated additional features for expanded capabilities. For example,  
30 the PrimOU primer selection program (available to the public from the Genome Center at University of Texas South West Medical Center, Dallas TX) is capable of choosing specific primers from megabase sequences and is thus useful for designing primers on a genome-wide scope. The Primer3 primer selection program (available to the public from the Whitehead Institute/MIT Center for Genome Research, Cambridge MA) allows the user to input a "mispriming library," in which  
35 sequences to avoid as primer binding sites are user-specified. Primer3 is useful, in particular, for

the selection of oligonucleotides for microarrays. (The source code for the latter two primer selection programs may also be obtained from their respective sources and modified to meet the user's specific needs.) The PrimeGen program (available to the public from the UK Human Genome Mapping Project Resource Centre, Cambridge UK) designs primers based on multiple  
5 sequence alignments, thereby allowing selection of primers that hybridize to either the most conserved or least conserved regions of aligned nucleic acid sequences. Hence, this program is useful for identification of both unique and conserved oligonucleotides and polynucleotide fragments. The oligonucleotides and polynucleotide fragments identified by any of the above selection methods are useful in hybridization technologies, for example, as PCR or sequencing  
10 primers, microarray elements, or specific probes to identify fully or partially complementary polynucleotides in a sample of nucleic acids. Methods of oligonucleotide selection are not limited to those described above.

A "recombinant nucleic acid" is a sequence that is not naturally occurring or has a sequence that is made by an artificial combination of two or more otherwise separated segments of sequence.  
15 This artificial combination is often accomplished by chemical synthesis or, more commonly, by the artificial manipulation of isolated segments of nucleic acids, e.g., by genetic engineering techniques such as those described in Sambrook, supra. The term recombinant includes nucleic acids that have been altered solely by addition, substitution, or deletion of a portion of the nucleic acid. Frequently, a recombinant nucleic acid may include a nucleic acid sequence operably linked to a promoter  
20 sequence. Such a recombinant nucleic acid may be part of a vector that is used, for example, to transform a cell.

Alternatively, such recombinant nucleic acids may be part of a viral vector, e.g., based on a vaccinia virus, that could be used to vaccinate a mammal wherein the recombinant nucleic acid is expressed, inducing a protective immunological response in the mammal.

25 A "regulatory element" refers to a nucleic acid sequence usually derived from untranslated regions of a gene and includes enhancers, promoters, introns, and 5' and 3' untranslated regions (UTRs). Regulatory elements interact with host or viral proteins which control transcription, translation, or RNA stability.

"Reporter molecules" are chemical or biochemical moieties used for labeling a nucleic acid,  
30 amino acid, or antibody. Reporter molecules include radionuclides; enzymes; fluorescent, chemiluminescent, or chromogenic agents; substrates; cofactors; inhibitors; magnetic particles; and other moieties known in the art.

An "RNA equivalent," in reference to a DNA sequence, is composed of the same linear sequence of nucleotides as the reference DNA sequence with the exception that all occurrences of  
35 the nitrogenous base thymine are replaced with uracil, and the sugar backbone is composed of



ribose instead of deoxyribose.

The term "sample" is used in its broadest sense. A sample suspected of containing KAP, nucleic acids encoding KAP, or fragments thereof may comprise a bodily fluid; an extract from a cell, chromosome, organelle, or membrane isolated from a cell; a cell; genomic DNA, RNA, or 5 cDNA, in solution or bound to a substrate; a tissue; a tissue print; etc.

The terms "specific binding" and "specifically binding" refer to that interaction between a protein or peptide and an agonist, an antibody, an antagonist, a small molecule, or any natural or synthetic binding composition. The interaction is dependent upon the presence of a particular structure of the protein, e.g., the antigenic determinant or epitope, recognized by the binding 10 molecule. For example, if an antibody is specific for epitope "A," the presence of a polypeptide comprising the epitope A, or the presence of free unlabeled A, in a reaction containing free labeled A and the antibody will reduce the amount of labeled A that binds to the antibody.

The term "substantially purified" refers to nucleic acid or amino acid sequences that are removed from their natural environment and are isolated or separated, and are at least 60% free, 15 preferably at least 75% free, and most preferably at least 90% free from other components with which they are naturally associated.

A "substitution" refers to the replacement of one or more amino acid residues or nucleotides by different amino acid residues or nucleotides, respectively.

"Substrate" refers to any suitable rigid or semi-rigid support including membranes, filters, 20 chips, slides, wafers, fibers, magnetic or nonmagnetic beads, gels, tubing, plates, polymers, microparticles and capillaries. The substrate can have a variety of surface forms, such as wells, trenches, pins, channels and pores, to which polynucleotides or polypeptides are bound.

A "transcript image" or "expression profile" refers to the collective pattern of gene expression by a particular cell type or tissue under given conditions at a given time.

25 "Transformation" describes a process by which exogenous DNA is introduced into a recipient cell. Transformation may occur under natural or artificial conditions according to various methods well known in the art, and may rely on any known method for the insertion of foreign nucleic acid sequences into a prokaryotic or eukaryotic host cell. The method for transformation is selected based on the type of host cell being transformed and may include, but is not limited to, 30 bacteriophage or viral infection, electroporation, heat shock, lipofection, and particle bombardment. The term "transformed cells" includes stably transformed cells in which the inserted DNA is capable of replication either as an autonomously replicating plasmid or as part of the host chromosome, as well as transiently transformed cells which express the inserted DNA or RNA for limited periods of time.

35 A "transgenic organism," as used herein, is any organism, including but not limited to

animals and plants, in which one or more of the cells of the organism contains heterologous nucleic acid introduced by way of human intervention, such as by transgenic techniques well known in the art. The nucleic acid is introduced into the cell, directly or indirectly by introduction into a precursor of the cell, by way of deliberate genetic manipulation, such as by microinjection or by infection with a recombinant virus. The term genetic manipulation does not include classical cross-breeding, or *in vitro* fertilization, but rather is directed to the introduction of a recombinant DNA molecule. The transgenic organisms contemplated in accordance with the present invention include bacteria, cyanobacteria, fungi, plants and animals. The isolated DNA of the present invention can be introduced into the host by methods known in the art, for example infection, transfection, transformation or transconjugation. Techniques for transferring the DNA of the present invention into such organisms are widely known and provided in references such as Sambrook et al. (1989), *supra*.

A "variant" of a particular nucleic acid sequence is defined as a nucleic acid sequence having at least 40% sequence identity to the particular nucleic acid sequence over a certain length of one of the nucleic acid sequences using blastn with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such a pair of nucleic acids may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% or greater sequence identity over a certain defined length. A variant may be described as, for example, an "allelic" (as defined above), "splice," "species," or "polymorphic" variant. A splice variant may have significant identity to a reference molecule, but will generally have a greater or lesser number of polynucleotides due to alternate splicing of exons during mRNA processing. The corresponding polypeptide may possess additional functional domains or lack domains that are present in the reference molecule. Species variants are polynucleotide sequences that vary from one species to another. The resulting polypeptides will generally have significant amino acid identity relative to each other. A polymorphic variant is a variation in the polynucleotide sequence of a particular gene between individuals of a given species. Polymorphic variants also may encompass "single nucleotide polymorphisms" (SNPs) in which the polynucleotide sequence varies by one nucleotide base. The presence of SNPs may be indicative of, for example, a certain population, a disease state, or a propensity for a disease state.

A "variant" of a particular polypeptide sequence is defined as a polypeptide sequence having at least 40% sequence identity to the particular polypeptide sequence over a certain length of one of the polypeptide sequences using blastp with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such a pair of polypeptides may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 91%, at least 92%, at least

93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% or greater sequence identity over a certain defined length of one of the polypeptides.

## THE INVENTION

5 The invention is based on the discovery of new human kinases and phosphatases (KAP), the polynucleotides encoding KAP, and the use of these compositions for the diagnosis, treatment, or prevention of cardiovascular diseases, immune system disorders, neurological disorders, disorders affecting growth and development, lipid disorders, cell proliferative disorders, and cancers.

Table 1 summarizes the nomenclature for the full length polynucleotide and polypeptide  
10 sequences of the invention. Each polynucleotide and its corresponding polypeptide are correlated to a single Incyte project identification number (Incyte Project ID). Each polypeptide sequence is denoted by both a polypeptide sequence identification number (Polypeptide SEQ ID NO:) and an Incyte polypeptide sequence number (Incyte Polypeptide ID) as shown. Each polynucleotide sequence is denoted by both a polynucleotide sequence identification number (Polynucleotide SEQ  
15 ID NO:) and an Incyte polynucleotide consensus sequence number (Incyte Polynucleotide ID) as shown.

Table 2 shows sequences with homology to the polypeptides of the invention as identified by BLAST analysis against the GenBank protein (genpept) database. Columns 1 and 2 show the polypeptide sequence identification number (Polypeptide SEQ ID NO:) and the corresponding  
20 Incyte polypeptide sequence number (Incyte Polypeptide ID) for polypeptides of the invention. Column 3 shows the GenBank identification number (GenBank ID NO:) of the nearest GenBank homolog. Column 4 shows the probability scores for the matches between each polypeptide and its homolog(s). Column 5 shows the annotation of the GenBank homolog(s) along with relevant citations where applicable, all of which are expressly incorporated by reference herein.

25 Table 3 shows various structural features of the polypeptides of the invention. Columns 1 and 2 show the polypeptide sequence identification number (SEQ ID NO:) and the corresponding Incyte polypeptide sequence number (Incyte Polypeptide ID) for each polypeptide of the invention. Column 3 shows the number of amino acid residues in each polypeptide. Column 4 shows potential phosphorylation sites, and column 5 shows potential glycosylation sites, as determined by the  
30 MOTIFS program of the GCG sequence analysis software package (Genetics Computer Group, Madison WI). Column 6 shows amino acid residues comprising signature sequences, domains, and motifs. Column 7 shows analytical methods for protein structure/function analysis and in some cases, searchable databases to which the analytical methods were applied.

Together, Tables 2 and 3 summarize the properties of polypeptides of the invention, and  
35 these properties establish that the claimed polypeptides are kinases and phosphatases. For example,

SEQ ID NO:1 is 79% identical to rat protein tyrosine phosphatase TD14 (GenBank ID g3598974) as determined by the Basic Local Alignment Search Tool (BLAST). (See Table 2.) The BLAST probability score is 0.0, which indicates the probability of obtaining the observed polypeptide sequence alignment by chance. SEQ ID NO:1 also contains protein-tyrosine phosphatase domain as determined by searching for statistically significant matches in the hidden Markov model (HMM)-based PFAM database of conserved protein family domains. (See Table 3.) Data from BLIMPS, PROFILESCAN and MOTIFS analyses provide further corroborative evidence that SEQ ID NO:1 is a protein-tyrosine phosphatase.

In an alternative example, SEQ ID NO:3 is 34% identical to Fagus sylvatica protein phosphatase 2C (PP2C, GenBank ID g7768151) as determined by the Basic Local Alignment Search Tool (BLAST). (See Table 2.) The BLAST probability score is  $6.4e-17$ , which indicates the probability of obtaining the observed polypeptide sequence alignment by chance. SEQ ID NO:3 also shares 45% identity with a putative Caenorhabditis elegans PP2C (GenBank ID g2804429), based on BLAST analysis, with a probability score of  $2.4e-71$ . SEQ ID NO:3 contains protein phosphatase 2C domains as determined by searching for statistically significant matches in the hidden Markov model (HMM)-based PFAM database of conserved protein family domains. (See Table 3.) Data from BLIMPS analysis provide further corroborative evidence that SEQ ID NO:3 is a protein phosphatase 2C.

In an alternative example, SEQ ID NO:5 is 25% identical to human protein kinase PAK5 (GenBank ID g7649810) as determined by the Basic Local Alignment Search Tool (BLAST). (See Table 2.) The BLAST probability score is  $7.2e-14$ , which indicates the probability of obtaining the observed polypeptide sequence alignment by chance. SEQ ID NO:5 also contains a eukaryotic protein kinase domain as determined by searching for statistically significant matches in the hidden Markov model (HMM)-based PFAM database of conserved protein family domains. (See Table 3.) Data from TMAP analysis as well as BLIMPS and BLAST analyses of the PRODOM and DOMO databases provide further corroborative evidence that SEQ ID NO:5 is a membrane-bound kinase.

In an alternative example, SEQ ID NO:6 is 1511 amino acid residues in length and is 97% identical over 1494 residues to human MEK kinase I (GenBank ID g2815888) as determined by the Basic Local Alignment Search Tool (BLAST). (See Table 2.) The BLAST probability score is 0.0, which indicates the probability of obtaining the observed polypeptide sequence alignment by chance. SEQ ID NO:6 also contains a eukaryotic protein kinase domain as determined by searching for statistically significant matches in the hidden Markov model (HMM)-based PFAM database of conserved protein family domains. (See Table 3.) Data from BLIMPS, MOTIFS, and PROFILESCAN analyses provide further corroborative evidence that SEQ ID NO:6 is protein kinase.

In an alternative example, SEQ ID NO:9 is 87% identical to murine protein kinase

(GenBank ID g406058) as determined by the Basic Local Alignment Search Tool (BLAST). (See Table 2.) The BLAST probability score is 0.0, which indicates the probability of obtaining the observed polypeptide sequence alignment by chance. SEQ ID NO:9 also contains an eukaryotic protein kinase domain and a PDZ domain as determined by searching for statistically significant matches in the hidden Markov model (HMM)-based PFAM database of conserved protein family domains. (See Table 3.) Data from BLIMPS, MOTIFS, and PROFILESCAN analyses provide further corroborative evidence that SEQ ID NO:9 is a protein kinase.

In an alternative example, SEQ ID NO:16 is 61% identical to human mitogen-activated kinase kinase kinase 5 (GenBank ID g1679668) as determined by the Basic Local Alignment Search Tool (BLAST). (See Table 2.) The BLAST probability score is 0.0, which indicates the probability of obtaining the observed polypeptide sequence alignment by chance. SEQ ID NO:16 also contains a eukaryotic protein kinase domain as determined by searching for statistically significant matches in the hidden Markov model (HMM)-based PFAM database of conserved protein family domains. (See Table 3.) Data from BLIMPS, MOTIFS, and PROFILESCAN analyses provide further corroborative evidence that SEQ ID NO:16 is a mitogen activated protein kinase kinase kinase.

In an alternative example, SEQ ID NO:18 is 83% identical from residues 4 to 372 to mouse protein kinase (GenBank ID g406058) as determined by the Basic Local Alignment Search Tool (BLAST). (See Table 2.) The BLAST probability score is 0.0, which indicates the probability of obtaining the observed polypeptide sequence alignment by chance. SEQ ID NO:18 also contains a eukaryotic protein kinase domain and a PDZ domain as determined by searching for statistically significant matches in the hidden Markov model (HMM)-based PFAM database of conserved protein family domains. (See Table 3.) Data from BLIMPS, MOTIFS, and PROFILESCAN analyses provide further corroborative evidence that SEQ ID NO:18 is a serine/threonine protein kinase.

In an alternative example, SEQ ID NO:19 is 95% identical, from residue M1 to residue V988, to Rattus norvegicus mytonic dystrophy kinase-related Cdc42-binding kinase (GenBank ID g2736151) as determined by the Basic Local Alignment Search Tool (BLAST). (See Table 2.) The BLAST probability score is 0.0, which indicates the probability of obtaining the observed polypeptide sequence alignment by chance. SEQ ID NO:19 also contains a protein kinase C terminal domain and a eukaryotic protein kinase domain as determined by searching for statistically significant matches in the hidden Markov model (HMM)-based PFAM database of conserved protein family domains. (See Table 3.) Data from BLIMPS, MOTIFS, and additional BLAST analyses provide further corroborative evidence that SEQ ID NO:19 is a protein kinase.

SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:10-15, SEQ ID NO:17,

and SEQ ID NO:20 were analyzed and annotated in a similar manner. The algorithms and parameters for the analysis of SEQ ID NO:1-20 are described in Table 7.

As shown in Table 4, the full length polynucleotide sequences of the present invention were assembled using cDNA sequences or coding (exon) sequences derived from genomic DNA, or any combination of these two types of sequences. Column 1 lists the polynucleotide sequence identification number (Polynucleotide SEQ ID NO:), the corresponding Incyte polynucleotide consensus sequence number (Incyte ID) for each polynucleotide of the invention, and the length of each polynucleotide sequence in basepairs. Column 2 shows the nucleotide start (5') and stop (3') positions of the cDNA and/or genomic sequences used to assemble the full length polynucleotide sequences of the invention, and of fragments of the polynucleotide sequences which are useful, for example, in hybridization or amplification technologies that identify SEQ ID NO:21-40 or that distinguish between SEQ ID NO:21-40 and related polynucleotide sequences.

The polynucleotide fragments described in Column 2 of Table 4 may refer specifically, for example, to Incyte cDNAs derived from tissue-specific cDNA libraries or from pooled cDNA libraries. Alternatively, the polynucleotide fragments described in column 2 may refer to GenBank cDNAs or ESTs which contributed to the assembly of the full length polynucleotide sequences. In addition, the polynucleotide fragments described in column 2 may identify sequences derived from the ENSEMBL (The Sanger Centre, Cambridge, UK) database (*i.e.*, those sequences including the designation "ENST"). Alternatively, the polynucleotide fragments described in column 2 may be derived from the NCBI RefSeq Nucleotide Sequence Records Database (*i.e.*, those sequences including the designation "NM" or "NT") or the NCBI RefSeq Protein Sequence Records (*i.e.*, those sequences including the designation "NP"). Alternatively, the polynucleotide fragments described in column 2 may refer to assemblages of both cDNA and Genscan-predicted exons brought together by an "exon stitching" algorithm. For example, a polynucleotide sequence identified as FL\_XXXXXX\_N<sub>1</sub>\_N<sub>2</sub>\_YYYYY\_N<sub>3</sub>\_N<sub>4</sub> represents a "stitched" sequence in which XXXXXX is the identification number of the cluster of sequences to which the algorithm was applied, and YYYYY is the number of the prediction generated by the algorithm, and N<sub>1,2,3...</sub>, if present, represent specific exons that may have been manually edited during analysis (See Example V). Alternatively, the polynucleotide fragments in column 2 may refer to assemblages of exons brought together by an "exon-stretching" algorithm. For example, a polynucleotide sequence identified as FLXXXXXX\_gAAAAA\_gBBBBB\_1\_N is a "stretched" sequence, with XXXXXX being the Incyte project identification number, gAAAAA being the GenBank identification number of the human genomic sequence to which the "exon-stretching" algorithm was applied, gBBBBB being the GenBank identification number or NCBI RefSeq identification number of the nearest GenBank protein homolog, and N referring to specific exons (See Example V). In instances where a RefSeq

sequence was used as a protein homolog for the "exon-stretching" algorithm, a RefSeq identifier (denoted by "NM," "NP," or "NT") may be used in place of the GenBank identifier (*i.e.*, gBBBBB).

Alternatively, a prefix identifies component sequences that were hand-edited, predicted from genomic DNA sequences, or derived from a combination of sequence analysis methods. The following Table lists examples of component sequence prefixes and corresponding sequence analysis methods associated with the prefixes (see Example IV and Example V).

Prefix	Type of analysis and/or examples of programs
GNN, GFG, ENST	Exon prediction from genomic sequences using, for example, GENSCAN (Stanford University, CA, USA) or FGENES (Computer Genomics Group, The Sanger Centre, Cambridge, UK).
GBI	Hand-edited analysis of genomic sequences.
FL	Stitched or stretched genomic sequences (see Example V).
INCY	Full length transcript and exon prediction from mapping of EST sequences to the genome. Genomic location and EST composition data are combined to predict the exons and resulting transcript.

In some cases, Incyte cDNA coverage redundant with the sequence coverage shown in Table 4 was obtained to confirm the final consensus polynucleotide sequence, but the relevant Incyte cDNA identification numbers are not shown.

Table 5 shows the representative cDNA libraries for those full length polynucleotide sequences which were assembled using Incyte cDNA sequences. The representative cDNA library is the Incyte cDNA library which is most frequently represented by the Incyte cDNA sequences which were used to assemble and confirm the above polynucleotide sequences. The tissues and vectors which were used to construct the cDNA libraries shown in Table 5 are described in Table 6.

The invention also encompasses KAP variants. A preferred KAP variant is one which has at least about 80%, or alternatively at least about 90%, or even at least about 95% amino acid sequence identity to the KAP amino acid sequence, and which contains at least one functional or structural characteristic of KAP.

The invention also encompasses polynucleotides which encode KAP. In a particular embodiment, the invention encompasses a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:21-40, which encodes KAP. The polynucleotide sequences of SEQ ID NO:21-40, as presented in the Sequence Listing, embrace the equivalent RNA sequences, wherein occurrences of the nitrogenous base thymine are replaced with uracil, and the sugar backbone is composed of ribose instead of deoxyribose.

The invention also encompasses a variant of a polynucleotide sequence encoding KAP. In

particular, such a variant polynucleotide sequence will have at least about 70%, or alternatively at least about 85%, or even at least about 95% polynucleotide sequence identity to the polynucleotide sequence encoding KAP. A particular aspect of the invention encompasses a variant of a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID  
5 NO:21-40 which has at least about 70%, or alternatively at least about 85%, or even at least about 95% polynucleotide sequence identity to a nucleic acid sequence selected from the group consisting of SEQ ID NO:21-40. Any one of the polynucleotide variants described above can encode an amino acid sequence which contains at least one functional or structural characteristic of KAP.

In addition, or in the alternative, a polynucleotide variant of the invention is a splice variant  
10 of a polynucleotide sequence encoding KAP. A splice variant may have portions which have significant sequence identity to the polynucleotide sequence encoding KAP, but will generally have a greater or lesser number of polynucleotides due to additions or deletions of blocks of sequence arising from alternate splicing of exons during mRNA processing. A splice variant may have less than about 70%, or alternatively less than about 60%, or alternatively less than about 50%  
15 polynucleotide sequence identity to the polynucleotide sequence encoding KAP over its entire length; however, portions of the splice variant will have at least about 70%, or alternatively at least about 85%, or alternatively at least about 95%, or alternatively 100% polynucleotide sequence identity to portions of the polynucleotide sequence encoding KAP. Any one of the splice variants described above can encode an amino acid sequence which contains at least one functional or  
20 structural characteristic of KAP.

It will be appreciated by those skilled in the art that as a result of the degeneracy of the genetic code, a multitude of polynucleotide sequences encoding KAP, some bearing minimal similarity to the polynucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention contemplates each and every possible variation of polynucleotide  
25 sequence that could be made by selecting combinations based on possible codon choices. These combinations are made in accordance with the standard triplet genetic code as applied to the polynucleotide sequence of naturally occurring KAP, and all such variations are to be considered as being specifically disclosed.

Although nucleotide sequences which encode KAP and its variants are generally capable of  
30 hybridizing to the nucleotide sequence of the naturally occurring KAP under appropriately selected conditions of stringency, it may be advantageous to produce nucleotide sequences encoding KAP or its derivatives possessing a substantially different codon usage, e.g., inclusion of non-naturally occurring codons. Codons may be selected to increase the rate at which expression of the peptide occurs in a particular prokaryotic or eukaryotic host in accordance with the frequency with which  
35 particular codons are utilized by the host. Other reasons for substantially altering the nucleotide



sequence encoding KAP and its derivatives without altering the encoded amino acid sequences include the production of RNA transcripts having more desirable properties, such as a greater half-life, than transcripts produced from the naturally occurring sequence.

The invention also encompasses production of DNA sequences which encode KAP and 5 KAP derivatives, or fragments thereof, entirely by synthetic chemistry. After production, the synthetic sequence may be inserted into any of the many available expression vectors and cell systems using reagents well known in the art. Moreover, synthetic chemistry may be used to introduce mutations into a sequence encoding KAP or any fragment thereof.

Also encompassed by the invention are polynucleotide sequences that are capable of 10 hybridizing to the claimed polynucleotide sequences, and, in particular, to those shown in SEQ ID NO:21-40 and fragments thereof under various conditions of stringency. (See, e.g., Wahl, G.M. and S.L. Berger (1987) *Methods Enzymol.* 152:399-407; Kimmel, A.R. (1987) *Methods Enzymol.* 152:507-511.) Hybridization conditions, including annealing and wash conditions, are described in "Definitions."

15 Methods for DNA sequencing are well known in the art and may be used to practice any of the embodiments of the invention. The methods may employ such enzymes as the Klenow fragment of DNA polymerase I, SEQUENASE (US Biochemical, Cleveland OH), Taq polymerase (Applied Biosystems), thermostable T7 polymerase (Amersham Pharmacia Biotech, Piscataway NJ), or combinations of polymerases and proofreading exonucleases such as those found in the 20 ELONGASE amplification system (Life Technologies, Gaithersburg MD). Preferably, sequence preparation is automated with machines such as the MICROLAB 2200 liquid transfer system (Hamilton, Reno NV), PTC200 thermal cycler (MJ Research, Watertown MA) and ABI CATALYST 800 thermal cycler (Applied Biosystems). Sequencing is then carried out using either the ABI 373 or 377 DNA sequencing system (Applied Biosystems), the MEGABACE 1000 DNA 25 sequencing system (Molecular Dynamics, Sunnyvale CA), or other systems known in the art. The resulting sequences are analyzed using a variety of algorithms which are well known in the art. (See, e.g., Ausubel, F.M. (1997) Short Protocols in Molecular Biology, John Wiley & Sons, New York NY, unit 7.7; Meyers, R.A. (1995) Molecular Biology and Biotechnology, Wiley VCH, New York NY, pp. 856-853.)

30 The nucleic acid sequences encoding KAP may be extended utilizing a partial nucleotide sequence and employing various PCR-based methods known in the art to detect upstream sequences, such as promoters and regulatory elements. For example, one method which may be employed, restriction-site PCR, uses universal and nested primers to amplify unknown sequence from genomic DNA within a cloning vector. (See, e.g., Sarkar, G. (1993) *PCR Methods Applic.* 35 2:318-322.) Another method, inverse PCR, uses primers that extend in divergent directions to

amplify unknown sequence from a circularized template. The template is derived from restriction fragments comprising a known genomic locus and surrounding sequences. (See, e.g., Triglia, T. et al. (1988) *Nucleic Acids Res.* 16:8186.) A third method, capture PCR, involves PCR amplification of DNA fragments adjacent to known sequences in human and yeast artificial chromosome DNA. 5 (See, e.g., Lagerstrom, M. et al. (1991) *PCR Methods Applic.* 1:111-119.) In this method, multiple restriction enzyme digestions and ligations may be used to insert an engineered double-stranded sequence into a region of unknown sequence before performing PCR. Other methods which may be used to retrieve unknown sequences are known in the art. (See, e.g., Parker, J.D. et al. (1991) *Nucleic Acids Res.* 19:3055-3060). Additionally, one may use PCR, nested primers, and 10 PROMOTERFINDER libraries (Clontech, Palo Alto CA) to walk genomic DNA. This procedure avoids the need to screen libraries and is useful in finding intron/exon junctions. For all PCR-based methods, primers may be designed using commercially available software, such as OLIGO 4.06 primer analysis software (National Biosciences, Plymouth MN) or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal 15 to the template at temperatures of about 68°C to 72°C.

When screening for full length cDNAs, it is preferable to use libraries that have been size-selected to include larger cDNAs. In addition, random-primed libraries, which often include sequences containing the 5' regions of genes, are preferable for situations in which an oligo d(T) library does not yield a full-length cDNA. Genomic libraries may be useful for extension of 20 sequence into 5' non-transcribed regulatory regions.

Capillary electrophoresis systems which are commercially available may be used to analyze the size or confirm the nucleotide sequence of sequencing or PCR products. In particular, capillary sequencing may employ flowable polymers for electrophoretic separation, four different nucleotide-specific, laser-stimulated fluorescent dyes, and a charge coupled device camera for detection of the 25 emitted wavelengths. Output/light intensity may be converted to electrical signal using appropriate software (e.g., GENOTYPER and SEQUENCE NAVIGATOR, Applied Biosystems), and the entire process from loading of samples to computer analysis and electronic data display may be computer controlled. Capillary electrophoresis is especially preferable for sequencing small DNA fragments which may be present in limited amounts in a particular sample.

30 In another embodiment of the invention, polynucleotide sequences or fragments thereof which encode KAP may be cloned in recombinant DNA molecules that direct expression of KAP, or fragments or functional equivalents thereof, in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences which encode substantially the same or a functionally equivalent amino acid sequence may be produced and used to express KAP.

35 The nucleotide sequences of the present invention can be engineered using methods

generally known in the art in order to alter KAP-encoding sequences for a variety of purposes including, but not limited to, modification of the cloning, processing, and/or expression of the gene product. DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. For example, 5 oligonucleotide-mediated site-directed mutagenesis may be used to introduce mutations that create new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, and so forth.

The nucleotides of the present invention may be subjected to DNA shuffling techniques such as MOLECULARBREEDING (Maxygen Inc., Santa Clara CA; described in U.S. Patent No. 10 5,837,458; Chang, C.-C. et al. (1999) Nat. Biotechnol. 17:793-797; Christians, F.C. et al. (1999) Nat. Biotechnol. 17:259-264; and Cramer, A. et al. (1996) Nat. Biotechnol. 14:315-319) to alter or improve the biological properties of KAP, such as its biological or enzymatic activity or its ability to bind to other molecules or compounds. DNA shuffling is a process by which a library of gene variants is produced using PCR-mediated recombination of gene fragments. The library is then 15 subjected to selection or screening procedures that identify those gene variants with the desired properties. These preferred variants may then be pooled and further subjected to recursive rounds of DNA shuffling and selection/screening. Thus, genetic diversity is created through "artificial" breeding and rapid molecular evolution. For example, fragments of a single gene containing random point mutations may be recombined, screened, and then reshuffled until the desired 20 properties are optimized. Alternatively, fragments of a given gene may be recombined with fragments of homologous genes in the same gene family, either from the same or different species, thereby maximizing the genetic diversity of multiple naturally occurring genes in a directed and controllable manner.

In another embodiment, sequences encoding KAP may be synthesized, in whole or in part, 25 using chemical methods well known in the art. (See, e.g., Caruthers, M.H. et al. (1980) Nucleic Acids Symp. Ser. 7:215-223; and Horn, T. et al. (1980) Nucleic Acids Symp. Ser. 7:225-232.) Alternatively, KAP itself or a fragment thereof may be synthesized using chemical methods. For example, peptide synthesis can be performed using various solution-phase or solid-phase techniques. (See, e.g., Creighton, T. (1984) Proteins, Structures and Molecular Properties, WH 30 Freeman, New York NY, pp. 55-60; and Roberge, J.Y. et al. (1995) Science 269:202-204.)

Automated synthesis may be achieved using the ABI 431A peptide synthesizer (Applied Biosystems). Additionally, the amino acid sequence of KAP, or any part thereof, may be altered during direct synthesis and/or combined with sequences from other proteins, or any part thereof, to produce a variant polypeptide or a polypeptide having a sequence of a naturally occurring 35 polypeptide.

The peptide may be substantially purified by preparative high performance liquid chromatography. (See, e.g., Chiez, R.M. and F.Z. Regnier (1990) *Methods Enzymol.* 182:392-421.) The composition of the synthetic peptides may be confirmed by amino acid analysis or by sequencing. (See, e.g., Creighton, *supra*, pp. 28-53.)

5 In order to express a biologically active KAP, the nucleotide sequences encoding KAP or derivatives thereof may be inserted into an appropriate expression vector, i.e., a vector which contains the necessary elements for transcriptional and translational control of the inserted coding sequence in a suitable host. These elements include regulatory sequences, such as enhancers, constitutive and inducible promoters, and 5' and 3' untranslated regions in the vector and in  
10 polynucleotide sequences encoding KAP. Such elements may vary in their strength and specificity. Specific initiation signals may also be used to achieve more efficient translation of sequences encoding KAP. Such signals include the ATG initiation codon and adjacent sequences, e.g. the Kozak sequence. In cases where sequences encoding KAP and its initiation codon and upstream regulatory sequences are inserted into the appropriate expression vector, no additional  
15 transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a fragment thereof, is inserted, exogenous translational control signals including an in-frame ATG initiation codon should be provided by the vector. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers appropriate for the particular host cell  
20 system used. (See, e.g., Scharf, D. et al. (1994) *Results Probl. Cell Differ.* 20:125-162.)

Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding KAP and appropriate transcriptional and translational control elements. These methods include *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. (See, e.g., Sambrook, J. et al. (1989)  
25 Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview NY, ch. 4, 8, and 16-17; Ausubel, F.M. et al. (1995) Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, ch. 9, 13, and 16.)

A variety of expression vector/host systems may be utilized to contain and express sequences encoding KAP. These include, but are not limited to, microorganisms such as bacteria  
30 transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with viral expression vectors (e.g., baculovirus); plant cell systems transformed with viral expression vectors (e.g., cauliflower mosaic virus, CaMV, or tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or animal cell systems. (See, e.g., Sambrook, *supra*; Ausubel, *supra*; Van  
35 Heeke, G. and S.M. Schuster (1989) *J. Biol. Chem.* 264:5503-5509; Engelhard, E.K. et al. (1994)

Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945; Takamatsu, N. (1987) EMBO J. 6:307-311; The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY, pp. 191-196; Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. USA 81:3655-3659; and Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355.) Expression  
 5 vectors derived from retroviruses, adenoviruses, or herpes or vaccinia viruses, or from various bacterial plasmids, may be used for delivery of nucleotide sequences to the targeted organ, tissue, or cell population. (See, e.g., Di Nicola, M. et al. (1998) Cancer Gen. Ther. 5(6):350-356; Yu, M. et al. (1993) Proc. Natl. Acad. Sci. USA 90(13):6340-6344; Buller, R.M. et al. (1985) Nature 317(6040):813-815; McGregor, D.P. et al. (1994) Mol. Immunol. 31(3):219-226; and Verma, I.M.  
 10 and N. Somia (1997) Nature 389:239-242.) The invention is not limited by the host cell employed.

In bacterial systems, a number of cloning and expression vectors may be selected depending upon the use intended for polynucleotide sequences encoding KAP. For example, routine cloning, subcloning, and propagation of polynucleotide sequences encoding KAP can be achieved using a multifunctional E. coli vector such as PBLUESCRIPT (Stratagene, La Jolla CA) or PSPORT1  
 15 plasmid (Life Technologies). Ligation of sequences encoding KAP into the vector's multiple cloning site disrupts the *lacZ* gene, allowing a colorimetric screening procedure for identification of transformed bacteria containing recombinant molecules. In addition, these vectors may be useful for in vitro transcription, dideoxy sequencing, single strand rescue with helper phage, and creation of nested deletions in the cloned sequence. (See, e.g., Van Heeke, G. and S.M. Schuster (1989) J.  
 20 Biol. Chem. 264:5503-5509.) When large quantities of KAP are needed, e.g. for the production of antibodies, vectors which direct high level expression of KAP may be used. For example, vectors containing the strong, inducible SP6 or T7 bacteriophage promoter may be used.

Yeast expression systems may be used for production of KAP. A number of vectors containing constitutive or inducible promoters, such as alpha factor, alcohol oxidase, and PGH  
 25 promoters, may be used in the yeast Saccharomyces cerevisiae or Pichia pastoris. In addition, such vectors direct either the secretion or intracellular retention of expressed proteins and enable integration of foreign sequences into the host genome for stable propagation. (See, e.g., Ausubel, 1995, supra; Bitter, G.A. et al. (1987) Methods Enzymol. 153:516-544; and Scorer, C.A. et al. (1994) Bio/Technology 12:181-184.)

30 Plant systems may also be used for expression of KAP. Transcription of sequences encoding KAP may be driven by viral promoters, e.g., the 35S and 19S promoters of CaMV used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) EMBO J. 6:307-311). Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used. (See, e.g., Coruzzi, G. et al. (1984) EMBO J. 3:1671-1680; Broglie, R. et  
 35 al. (1984) Science 224:838-843; and Winter, J. et al. (1991) Results Probl. Cell Differ. 17:85-105.)

These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. (See, e.g., The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY, pp. 191-196.)

In mammalian cells, a number of viral-based expression systems may be utilized. In cases  
5 where an adenovirus is used as an expression vector, sequences encoding KAP may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain infective virus which expresses KAP in host cells. (See, e.g., Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. USA 81:3655-3659.) In addition, transcription enhancers, such as the Rous  
10 sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells. SV40 or EBV-based vectors may also be used for high-level protein expression.

Human artificial chromosomes (HACs) may also be employed to deliver larger fragments of DNA than can be contained in and expressed from a plasmid. HACs of about 6 kb to 10 Mb are constructed and delivered via conventional delivery methods (liposomes, polycationic amino  
15 polymers, or vesicles) for therapeutic purposes. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355.)

For long term production of recombinant proteins in mammalian systems, stable expression of KAP in cell lines is preferred. For example, sequences encoding KAP can be transformed into cell lines using expression vectors which may contain viral origins of replication and/or endogenous  
20 expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for about 1 to 2 days in enriched media before being switched to selective media. The purpose of the selectable marker is to confer resistance to a selective agent, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be  
25 propagated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase and adenine phosphoribosyltransferase genes, for use in *tk*<sup>-</sup> and *apv*<sup>-</sup> cells, respectively. (See, e.g., Wigler, M. et al. (1977) Cell 11:223-232; Lowy, I. et al. (1980) Cell 22:817-823.) Also, antimetabolite, antibiotic,  
30 or herbicide resistance can be used as the basis for selection. For example, *dhfr* confers resistance to methotrexate; *neo* confers resistance to the aminoglycosides neomycin and G-418; and *als* and *pat* confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively. (See, e.g., Wigler, M. et al. (1980) Proc. Natl. Acad. Sci. USA 77:3567-3570; Colbere-Garapin, F. et al. (1981) J. Mol. Biol. 150:1-14.) Additional selectable genes have been described, e.g., *trpB* and *hisD*,  
35 which alter cellular requirements for metabolites. (See, e.g., Hartman, S.C. and R.C. Mulligan

(1988) Proc. Natl. Acad. Sci. USA 85:8047-8051.) Visible markers, e.g., anthocyanins, green fluorescent proteins (GFP; Clontech),  $\beta$  glucuronidase and its substrate  $\beta$ -glucuronide, or luciferase and its substrate luciferin may be used. These markers can be used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system. (See, e.g., Rhodes, C.A. (1995) Methods Mol. Biol. 55:121-131.)

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, the presence and expression of the gene may need to be confirmed. For example, if the sequence encoding KAP is inserted within a marker gene sequence, transformed cells containing sequences encoding KAP can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a sequence encoding KAP under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

In general, host cells that contain the nucleic acid sequence encoding KAP and that express KAP may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations, PCR amplification, and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein sequences.

Immunological methods for detecting and measuring the expression of KAP using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on KAP is preferred, but a competitive binding assay may be employed. These and other assays are well known in the art. (See, e.g., Hampton, R. et al. (1990) Serological Methods, a Laboratory Manual, APS Press, St. Paul MN, Sect. IV; Coligan, J.E. et al. (1997) Current Protocols in Immunology, Greene Pub. Associates and Wiley-Interscience, New York NY; and Pound, J.D. (1998) Immunochemical Protocols, Humana Press, Totowa NJ.)

A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides encoding KAP include oligolabeling, nick translation, end-labeling, or PCR amplification using a labeled nucleotide. Alternatively, the sequences encoding KAP, or any fragments thereof, may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes *in vitro* by addition of an

appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits, such as those provided by Amersham Pharmacia Biotech, Promega (Madison WI), and US Biochemical. Suitable reporter molecules or labels which may be used for ease of detection include radionuclides, enzymes, 5 fluorescent, chemiluminescent, or chromogenic agents, as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with nucleotide sequences encoding KAP may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a transformed cell may be secreted or retained intracellularly depending on the 10 sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides which encode KAP may be designed to contain signal sequences which direct secretion of KAP through a prokaryotic or eukaryotic cell membrane.

In addition, a host cell strain may be chosen for its ability to modulate expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of 15 the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" or "pro" form of the protein may also be used to specify protein targeting, folding, and/or activity. Different host cells which have specific cellular machinery and characteristic mechanisms for post-translational activities (e.g., CHO, HeLa, MDCK, HEK293, and WI38) are available from the 20 American Type Culture Collection (ATCC, Manassas VA) and may be chosen to ensure the correct modification and processing of the foreign protein.

In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences encoding KAP may be ligated to a heterologous sequence resulting in translation of a fusion protein in any of the aforementioned host systems. For example, a chimeric KAP protein 25 containing a heterologous moiety that can be recognized by a commercially available antibody may facilitate the screening of peptide libraries for inhibitors of KAP activity. Heterologous protein and peptide moieties may also facilitate purification of fusion proteins using commercially available affinity matrices. Such moieties include, but are not limited to, glutathione S-transferase (GST), maltose binding protein (MBP), thioredoxin (Trx), calmodulin binding peptide (CBP), 6-His, 30 FLAG, *c-myc*, and hemagglutinin (HA). GST, MBP, Trx, CBP, and 6-His enable purification of their cognate fusion proteins on immobilized glutathione, maltose, phenylarsine oxide, calmodulin, and metal-chelate resins, respectively. FLAG, *c-myc*, and hemagglutinin (HA) enable immunoaffinity purification of fusion proteins using commercially available monoclonal and polyclonal antibodies that specifically recognize these epitope tags. A fusion protein may also be 35 engineered to contain a proteolytic cleavage site located between the KAP encoding sequence and



the heterologous protein sequence, so that KAP may be cleaved away from the heterologous moiety following purification. Methods for fusion protein expression and purification are discussed in Ausubel (1995, supra, ch. 10). A variety of commercially available kits may also be used to facilitate expression and purification of fusion proteins.

5 In a further embodiment of the invention, synthesis of radiolabeled KAP may be achieved in vitro using the TNT rabbit reticulocyte lysate or wheat germ extract system (Promega). These systems couple transcription and translation of protein-coding sequences operably associated with the T7, T3, or SP6 promoters. Translation takes place in the presence of a radiolabeled amino acid precursor, for example, <sup>35</sup>S-methionine.

10 KAP of the present invention or fragments thereof may be used to screen for compounds that specifically bind to KAP. At least one and up to a plurality of test compounds may be screened for specific binding to KAP. Examples of test compounds include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

In one embodiment, the compound thus identified is closely related to the natural ligand of  
15 KAP, e.g., a ligand or fragment thereof, a natural substrate, a structural or functional mimetic, or a natural binding partner. (See, e.g., Coligan, J.E. et al. (1991) Current Protocols in Immunology 1(2): Chapter 5.) Similarly, the compound can be closely related to the natural receptor to which KAP binds, or to at least a fragment of the receptor, e.g., the ligand binding site. In either case, the compound can be rationally designed using known techniques. In one embodiment, screening for  
20 these compounds involves producing appropriate cells which express KAP, either as a secreted protein or on the cell membrane. Preferred cells include cells from mammals, yeast, Drosophila, or E. coli. Cells expressing KAP or cell membrane fractions which contain KAP are then contacted with a test compound and binding, stimulation, or inhibition of activity of either KAP or the compound is analyzed.

25 An assay may simply test binding of a test compound to the polypeptide, wherein binding is detected by a fluorophore, radioisotope, enzyme conjugate, or other detectable label. For example, the assay may comprise the steps of combining at least one test compound with KAP, either in solution or affixed to a solid support, and detecting the binding of KAP to the compound. Alternatively, the assay may detect or measure binding of a test compound in the presence of a  
30 labeled competitor. Additionally, the assay may be carried out using cell-free preparations, chemical libraries, or natural product mixtures, and the test compound(s) may be free in solution or affixed to a solid support.

KAP of the present invention or fragments thereof may be used to screen for compounds that modulate the activity of KAP. Such compounds may include agonists, antagonists, or partial or  
35 inverse agonists. In one embodiment, an assay is performed under conditions permissive for KAP

activity, wherein KAP is combined with at least one test compound, and the activity of KAP in the presence of a test compound is compared with the activity of KAP in the absence of the test compound. A change in the activity of KAP in the presence of the test compound is indicative of a compound that modulates the activity of KAP. Alternatively, a test compound is combined with an in vitro or cell-free system comprising KAP under conditions suitable for KAP activity, and the assay is performed. In either of these assays, a test compound which modulates the activity of KAP may do so indirectly and need not come in direct contact with the test compound. At least one and up to a plurality of test compounds may be screened.

In another embodiment, polynucleotides encoding KAP or their mammalian homologs may be "knocked out" in an animal model system using homologous recombination in embryonic stem (ES) cells. Such techniques are well known in the art and are useful for the generation of animal models of human disease. (See, e.g., U.S. Patent No. 5,175,383 and U.S. Patent No. 5,767,337.) For example, mouse ES cells, such as the mouse 129/SvJ cell line, are derived from the early mouse embryo and grown in culture. The ES cells are transformed with a vector containing the gene of interest disrupted by a marker gene, e.g., the neomycin phosphotransferase gene (neo; Capecchi, M.R. (1989) *Science* 244:1288-1292). The vector integrates into the corresponding region of the host genome by homologous recombination. Alternatively, homologous recombination takes place using the Cre-loxP system to knockout a gene of interest in a tissue- or developmental stage-specific manner (Marth, J.D. (1996) *Clin. Invest.* 97:1999-2002; Wagner, K.U. et al. (1997) *Nucleic Acids Res.* 25:4323-4330). Transformed ES cells are identified and microinjected into mouse cell blastocysts such as those from the C57BL/6 mouse strain. The blastocysts are surgically transferred to pseudopregnant dams, and the resulting chimeric progeny are genotyped and bred to produce heterozygous or homozygous strains. Transgenic animals thus generated may be tested with potential therapeutic or toxic agents.

Polynucleotides encoding KAP may also be manipulated in vitro in ES cells derived from human blastocysts. Human ES cells have the potential to differentiate into at least eight separate cell lineages including endoderm, mesoderm, and ectodermal cell types. These cell lineages differentiate into, for example, neural cells, hematopoietic lineages, and cardiomyocytes (Thomson, J.A. et al. (1998) *Science* 282:1145-1147).

Polynucleotides encoding KAP can also be used to create "knockin" humanized animals (pigs) or transgenic animals (mice or rats) to model human disease. With knockin technology, a region of a polynucleotide encoding KAP is injected into animal ES cells, and the injected sequence integrates into the animal cell genome. Transformed cells are injected into blastulae, and the blastulae are implanted as described above. Transgenic progeny or inbred lines are studied and treated with potential pharmaceutical agents to obtain information on treatment of a human disease.

Alternatively, a mammal inbred to overexpress KAP, e.g., by secreting KAP in its milk, may also serve as a convenient source of that protein (Janne, J. et al. (1998) *Biotechnol. Annu. Rev.* 4:55-74).

## THERAPEUTICS

Chemical and structural similarity, e.g., in the context of sequences and motifs, exists  
5 between regions of KAP and kinases and phosphatases. In addition, examples of tissues expressing KAP can be found in Table 6. Therefore, KAP appears to play a role in cardiovascular diseases, immune system disorders, neurological disorders, disorders affecting growth and development, lipid disorders, cell proliferative disorders, and cancers. In the treatment of disorders associated with increased KAP expression or activity, it is desirable to decrease the expression or activity of KAP.  
10 In the treatment of disorders associated with decreased KAP expression or activity, it is desirable to increase the expression or activity of KAP.

Therefore, in one embodiment, KAP or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of KAP. Examples of such disorders include, but are not limited to, a cardiovascular  
15 disorder such as arteriovenous fistula, atherosclerosis, hypertension, vasculitis, Raynaud's disease, aneurysms, arterial dissections, varicose veins, thrombophlebitis and phlebothrombosis, vascular tumors, and complications of thrombolysis, balloon angioplasty, vascular replacement, and coronary artery bypass graft surgery, congestive heart failure, ischemic heart disease, angina pectoris, myocardial infarction, hypertensive heart disease, degenerative valvular heart disease, calcific aortic  
20 valve stenosis, congenitally bicuspid aortic valve, mitral annular calcification, mitral valve prolapse, rheumatic fever and rheumatic heart disease, infective endocarditis, nonbacterial thrombotic endocarditis, endocarditis of systemic lupus erythematosus, carcinoid heart disease, cardiomyopathy, myocarditis, pericarditis, neoplastic heart disease, congenital heart disease, and complications of cardiac transplantation, congenital lung anomalies, atelectasis, pulmonary  
25 congestion and edema, pulmonary embolism, pulmonary hemorrhage, pulmonary infarction, pulmonary hypertension, vascular sclerosis, obstructive pulmonary disease, restrictive pulmonary disease, chronic obstructive pulmonary disease, emphysema, chronic bronchitis, bronchial asthma, bronchiectasis, bacterial pneumonia, viral and mycoplasmal pneumonia, lung abscess, pulmonary tuberculosis, diffuse interstitial diseases, pneumoconioses, sarcoidosis, idiopathic pulmonary  
30 fibrosis, desquamative interstitial pneumonitis, hypersensitivity pneumonitis, pulmonary eosinophilia bronchiolitis obliterans-organizing pneumonia, diffuse pulmonary hemorrhage syndromes, Goodpasture's syndromes, idiopathic pulmonary hemosiderosis, pulmonary involvement in collagen-vascular disorders, pulmonary alveolar proteinosis, lung tumors, inflammatory and noninflammatory pleural effusions, pneumothorax, pleural tumors, drug-induced lung disease,  
35 radiation-induced lung disease, and complications of lung transplantation; an immune disorder such

as acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, and trauma; a neurological disorder such as epilepsy, ischemic cerebrovascular disease, stroke, cerebral neoplasms, Alzheimer's disease, Pick's disease, Huntington's disease, dementia, Parkinson's disease and other extrapyramidal disorders, amyotrophic lateral sclerosis and other motor neuron disorders, progressive neural muscular atrophy, retinitis pigmentosa, hereditary ataxias, multiple sclerosis and other demyelinating diseases, bacterial and viral meningitis, brain abscess, subdural empyema, epidural abscess, suppurative intracranial thrombophlebitis, myelitis and radiculitis, viral central nervous system disease, prion diseases including kuru, Creutzfeldt-Jakob disease, and Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia, nutritional and metabolic diseases of the nervous system, neurofibromatosis, tuberous sclerosis, cerebelloretinal hemangioblastomatosis, encephalotrigeminal syndrome, mental retardation and other developmental disorders of the central nervous system including Down syndrome, cerebral palsy, neuroskeletal disorders, autonomic nervous system disorders, cranial nerve disorders, spinal cord diseases, muscular dystrophy and other neuromuscular disorders, peripheral nervous system disorders, dermatomyositis and polymyositis, inherited, metabolic, endocrine, and toxic myopathies, myasthenia gravis, periodic paralysis, mental disorders including mood, anxiety, and schizophrenic disorders, seasonal affective disorder (SAD), akathisia, amnesia, catatonia, diabetic neuropathy, tardive dyskinesia, dystonias, paranoid psychoses, postherpetic neuralgia, Tourette's disorder, progressive supranuclear palsy, corticobasal degeneration, and familial frontotemporal dementia; a growth and developmental disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, renal tubular acidosis, anemia, Cushing's syndrome, achondroplastic dwarfism, Duchenne and Becker muscular dystrophy, epilepsy, gonadal

dysgenesis, WAGR syndrome (Wilms' tumor, aniridia, genitourinary abnormalities, and mental retardation), Smith-Magenis syndrome, myelodysplastic syndrome, hereditary mucoepithelial dysplasia, hereditary keratodermas, hereditary neuropathies such as Charcot-Marie-Tooth disease and neurofibromatosis, hypothyroidism, hydrocephalus, seizure disorders such as Sydenham's chorea and cerebral palsy, spina bifida, anencephaly, craniorachischisis, congenital glaucoma, cataract, and sensorineural hearing loss; a lipid disorder such as fatty liver, cholestasis, primary biliary cirrhosis, carnitine deficiency, carnitine palmitoyltransferase deficiency, myoadenylate deaminase deficiency, hypertriglyceridemia, lipid storage disorders such as Fabry's disease, Gaucher's disease, Niemann-Pick's disease, metachromatic leukodystrophy, adrenoleukodystrophy, GM<sub>2</sub> gangliosidosis, and ceroid lipofuscinosis, abetalipoproteinemia, Tangier disease, hyperlipoproteinemia, diabetes mellitus, lipodystrophy, lipomatosis, acute panniculitis, disseminated fat necrosis, adiposis dolorosa, lipoid adrenal hyperplasia, minimal change disease, lipomas, atherosclerosis, hypercholesterolemia, hypercholesterolemia with hypertriglyceridemia, primary hypoalphalipoproteinemia, hypothyroidism, renal disease, liver disease, lecithin:cholesterol acyltransferase deficiency, cerebrotendinous xanthomatosis, sitosterolemia, hypocholesterolemia, Tay-Sachs disease, Sandhoff's disease, hyperlipidemia, hyperlipemia, lipid myopathies, and obesity; and a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, uterus, leukemias such as multiple myeloma, and lymphomas such as Hodgkin's disease..

25 In another embodiment, a vector capable of expressing KAP or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of KAP including, but not limited to, those described above.

In a further embodiment, a composition comprising a substantially purified KAP in conjunction with a suitable pharmaceutical carrier may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of KAP including, but not limited to, those provided above.

In still another embodiment, an agonist which modulates the activity of KAP may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of KAP including, but not limited to, those listed above.

35 In a further embodiment, an antagonist of KAP may be administered to a subject to treat or

prevent a disorder associated with increased expression or activity of KAP. Examples of such disorders include, but are not limited to, those cardiovascular diseases, immune system disorders, neurological disorders, disorders affecting growth and development, lipid disorders, cell proliferative disorders, and cancers described above. In one aspect, an antibody which specifically binds KAP may be used directly as an antagonist or indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissues which express KAP.

In an additional embodiment, a vector expressing the complement of the polynucleotide encoding KAP may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of KAP including, but not limited to, those described above.

10 In other embodiments, any of the proteins, antagonists, antibodies, agonists, complementary sequences, or vectors of the invention may be administered in combination with other appropriate therapeutic agents. Selection of the appropriate agents for use in combination therapy may be made by one of ordinary skill in the art, according to conventional pharmaceutical principles. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders described above. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

An antagonist of KAP may be produced using methods which are generally known in the art. In particular, purified KAP may be used to produce antibodies or to screen libraries of pharmaceutical agents to identify those which specifically bind KAP. Antibodies to KAP may also be generated using methods that are well known in the art. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, and single chain antibodies, Fab fragments, and fragments produced by a Fab expression library. Neutralizing antibodies (i.e., those which inhibit dimer formation) are generally preferred for therapeutic use.

For the production of antibodies, various hosts including goats, rabbits, rats, mice, humans, and others may be immunized by injection with KAP or with any fragment or oligopeptide thereof which has immunogenic properties. Depending on the host species, various adjuvants may be used to increase immunological response. Such adjuvants include, but are not limited to, Freund's, mineral gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, KLH, and dinitrophenol. Among adjuvants used in humans, BCG (bacilli Calmette-Guerin) and Corynebacterium parvum are especially preferable.

It is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to KAP have an amino acid sequence consisting of at least about 5 amino acids, and generally will consist of at least about 10 amino acids. It is also preferable that these oligopeptides, peptides, or fragments are identical to a portion of the amino acid sequence of the natural protein. Short

stretches of KAP amino acids may be fused with those of another protein, such as KLH, and antibodies to the chimeric molecule may be produced.

Monoclonal antibodies to KAP may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV-hybridoma technique. (See, e.g., Kohler, G. et al. (1975) *Nature* 256:495-497; Kozbor, D. et al. (1985) *J. Immunol. Methods* 81:31-42; Cote, R.J. et al. (1983) *Proc. Natl. Acad. Sci. USA* 80:2026-2030; and Cole, S.P. et al. (1984) *Mol. Cell Biol.* 62:109-120.)

In addition, techniques developed for the production of "chimeric antibodies," such as the splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate antigen specificity and biological activity, can be used. (See, e.g., Morrison, S.L. et al. (1984) *Proc. Natl. Acad. Sci. USA* 81:6851-6855; Neuberger, M.S. et al. (1984) *Nature* 312:604-608; and Takeda, S. et al. (1985) *Nature* 314:452-454.) Alternatively, techniques described for the production of single chain antibodies may be adapted, using methods known in the art, to produce KAP-specific single chain antibodies. Antibodies with related specificity, but of distinct idiotypic composition, may be generated by chain shuffling from random combinatorial immunoglobulin libraries. (See, e.g., Burton, D.R. (1991) *Proc. Natl. Acad. Sci. USA* 88:10134-10137.)

Antibodies may also be produced by inducing *in vivo* production in the lymphocyte population or by screening immunoglobulin libraries or panels of highly specific binding reagents as disclosed in the literature. (See, e.g., Orlandi, R. et al. (1989) *Proc. Natl. Acad. Sci. USA* 86:3833-3837; Winter, G. et al. (1991) *Nature* 349:293-299.)

Antibody fragments which contain specific binding sites for KAP may also be generated. For example, such fragments include, but are not limited to,  $F(ab')_2$  fragments produced by pepsin digestion of the antibody molecule and Fab fragments generated by reducing the disulfide bridges of the  $F(ab')_2$  fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity. (See, e.g., Huse, W.D. et al. (1989) *Science* 246:1275-1281.)

Various immunoassays may be used for screening to identify antibodies having the desired specificity. Numerous protocols for competitive binding or immunoradiometric assays using either polyclonal or monoclonal antibodies with established specificities are well known in the art. Such immunoassays typically involve the measurement of complex formation between KAP and its specific antibody. A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering KAP epitopes is generally used, but a competitive binding assay may also be employed (Pound, *supra*).

Various methods such as Scatchard analysis in conjunction with radioimmunoassay

techniques may be used to assess the affinity of antibodies for KAP. Affinity is expressed as an association constant,  $K_a$ , which is defined as the molar concentration of KAP-antibody complex divided by the molar concentrations of free antigen and free antibody under equilibrium conditions. The  $K_a$  determined for a preparation of polyclonal antibodies, which are heterogeneous in their 5 affinities for multiple KAP epitopes, represents the average affinity, or avidity, of the antibodies for KAP. The  $K_a$  determined for a preparation of monoclonal antibodies, which are monospecific for a particular KAP epitope, represents a true measure of affinity. High-affinity antibody preparations with  $K_a$  ranging from about  $10^9$  to  $10^{12}$  L/mole are preferred for use in immunoassays in which the KAP-antibody complex must withstand rigorous manipulations. Low-affinity antibody preparations 10 with  $K_a$  ranging from about  $10^6$  to  $10^7$  L/mole are preferred for use in immunopurification and similar procedures which ultimately require dissociation of KAP, preferably in active form, from the antibody (Catty, D. (1988) Antibodies, Volume I: A Practical Approach, IRL Press, Washington DC; Liddell, J.E. and A. Cryer (1991) A Practical Guide to Monoclonal Antibodies, John Wiley & Sons, New York NY).

15 The titer and avidity of polyclonal antibody preparations may be further evaluated to determine the quality and suitability of such preparations for certain downstream applications. For example, a polyclonal antibody preparation containing at least 1-2 mg specific antibody/ml, preferably 5-10 mg specific antibody/ml, is generally employed in procedures requiring precipitation of KAP-antibody complexes. Procedures for evaluating antibody specificity, titer, and 20 avidity, and guidelines for antibody quality and usage in various applications, are generally available. (See, e.g., Catty, supra, and Coligan et al. supra.)

In another embodiment of the invention, the polynucleotides encoding KAP, or any fragment or complement thereof, may be used for therapeutic purposes. In one aspect, modifications of gene expression can be achieved by designing complementary sequences or 25 antisense molecules (DNA, RNA, PNA, or modified oligonucleotides) to the coding or regulatory regions of the gene encoding KAP. Such technology is well known in the art, and antisense oligonucleotides or larger fragments can be designed from various locations along the coding or control regions of sequences encoding KAP. (See, e.g., Agrawal, S., ed. (1996) Antisense Therapeutics, Humana Press Inc., Totawa NJ.)

30 In therapeutic use, any gene delivery system suitable for introduction of the antisense sequences into appropriate target cells can be used. Antisense sequences can be delivered intracellularly in the form of an expression plasmid which, upon transcription, produces a sequence complementary to at least a portion of the cellular sequence encoding the target protein. (See, e.g., Slater, J.E. et al. (1998) *J. Allergy Clin. Immunol.* 102(3):469-475; and Scanlon, K.J. et al. (1995) 35 9(13):1288-1296.) Antisense sequences can also be introduced intracellularly through the use of



viral vectors, such as retrovirus and adeno-associated virus vectors. (See, e.g., Miller, A.D. (1990) Blood 76:271; Ausubel, *supra*; Uckert, W. and W. Walther (1994) Pharmacol. Ther. 63(3):323-347.) Other gene delivery mechanisms include liposome-derived systems, artificial viral envelopes, and other systems known in the art. (See, e.g., Rossi, J.J. (1995) Br. Med. Bull. 51(1):217-225; 5 Boado, R.J. et al. (1998) J. Pharm. Sci. 87(11):1308-1315; and Morris, M.C. et al. (1997) Nucleic Acids Res. 25(14):2730-2736.)

In another embodiment of the invention, polynucleotides encoding KAP may be used for somatic or germline gene therapy. Gene therapy may be performed to (i) correct a genetic deficiency (e.g., in the cases of severe combined immunodeficiency (SCID)-X1 disease 10 characterized by X-linked inheritance (Cavazzana-Calvo, M. et al. (2000) Science 288:669-672), severe combined immunodeficiency syndrome associated with an inherited adenosine deaminase (ADA) deficiency (Blaese, R.M. et al. (1995) Science 270:475-480; Bordignon, C. et al. (1995) Science 270:470-475), cystic fibrosis (Zabner, J. et al. (1993) Cell 75:207-216; Crystal, R.G. et al. (1995) Hum. Gene Therapy 6:643-666; Crystal, R.G. et al. (1995) Hum. Gene Therapy 6:667-703), 15 thalassemias, familial hypercholesterolemia, and hemophilia resulting from Factor VIII or Factor IX deficiencies (Crystal, R.G. (1995) Science 270:404-410; Verma, I.M. and N. Somia (1997) Nature 389:239-242)), (ii) express a conditionally lethal gene product (e.g., in the case of cancers which result from unregulated cell proliferation), or (iii) express a protein which affords protection against intracellular parasites (e.g., against human retroviruses, such as human immunodeficiency virus 20 (HIV) (Baltimore, D. (1988) Nature 335:395-396; Poeschla, E. et al. (1996) Proc. Natl. Acad. Sci. USA 93:11395-11399), hepatitis B or C virus (HBV, HCV); fungal parasites, such as Candida albicans and Paracoccidioides brasiliensis; and protozoan parasites such as Plasmodium falciparum and Trypanosoma cruzi). In the case where a genetic deficiency in KAP expression or regulation causes disease, the expression of KAP from an appropriate population of transduced cells may 25 alleviate the clinical manifestations caused by the genetic deficiency.

In a further embodiment of the invention, diseases or disorders caused by deficiencies in KAP are treated by constructing mammalian expression vectors encoding KAP and introducing these vectors by mechanical means into KAP-deficient cells. Mechanical transfer technologies for use with cells *in vivo* or *ex vitro* include (i) direct DNA microinjection into individual cells, (ii) 30 ballistic gold particle delivery, (iii) liposome-mediated transfection, (iv) receptor-mediated gene transfer, and (v) the use of DNA transposons (Morgan, R.A. and W.F. Anderson (1993) Annu. Rev. Biochem. 62:191-217; Ivics, Z. (1997) Cell 91:501-510; Boulay, J.-L. and H. R  c  pon (1998) Curr. Opin. Biotechnol. 9:445-450).

Expression vectors that may be effective for the expression of KAP include, but are not 35 limited to, the PCDNA 3.1, EPITAG, PRCCMV2, PREP, PVAX, PCR2-TOPOTA vectors

(Invitrogen, Carlsbad CA), PCMV-SCRIPT, PCMV-TAG, PEGSH/PERV (Stratagene, La Jolla CA), and PTET-OFF, PTET-ON, PTRE2, PTRE2-LUC, PTK-HYG (Clontech, Palo Alto CA). KAP may be expressed using (i) a constitutively active promoter, (e.g., from cytomegalovirus (CMV), Rous sarcoma virus (RSV), SV40 virus, thymidine kinase (TK), or  $\beta$ -actin genes), (ii) 5 inducible promoter (e.g., the tetracycline-regulated promoter (Gossen, M. and H. Bujard (1992) Proc. Natl. Acad. Sci. USA 89:5547-5551; Gossen, M. et al. (1995) Science 268:1766-1769; Rossi, F.M.V. and H.M. Blau (1998) Curr. Opin. Biotechnol. 9:451-456), commercially available in the T-REX plasmid (Invitrogen)); the ecdysone-inducible promoter (available in the plasmids PVGRXR and PIND; Invitrogen); the FK506/rapamycin inducible promoter; or the RU486/mifepristone 10 inducible promoter (Rossi, F.M.V. and H.M. Blau, *supra*), or (iii) a tissue-specific promoter or the native promoter of the endogenous gene encoding KAP from a normal individual.

Commercially available liposome transformation kits (e.g., the PERFECT LIPID TRANSFECTION KIT, available from Invitrogen) allow one with ordinary skill in the art to deliver polynucleotides to target cells in culture and require minimal effort to optimize experimental 15 parameters. In the alternative, transformation is performed using the calcium phosphate method (Graham, F.L. and A.J. Eb (1973) Virology 52:456-467), or by electroporation (Neumann, E. et al. (1982) EMBO J. 1:841-845). The introduction of DNA to primary cells requires modification of these standardized mammalian transfection protocols.

In another embodiment of the invention, diseases or disorders caused by genetic defects 20 with respect to KAP expression are treated by constructing a retrovirus vector consisting of (i) the polynucleotide encoding KAP under the control of an independent promoter or the retrovirus long terminal repeat (LTR) promoter, (ii) appropriate RNA packaging signals, and (iii) a Rev-responsive element (RRE) along with additional retrovirus *cis*-acting RNA sequences and coding sequences required for efficient vector propagation. Retrovirus vectors (e.g., PFB and PFBNEO) are 25 commercially available (Stratagene) and are based on published data (Riviere, I. et al. (1995) Proc. Natl. Acad. Sci. USA 92:6733-6737), incorporated by reference herein. The vector is propagated in an appropriate vector producing cell line (VPCL) that expresses an envelope gene with a tropism for receptors on the target cells or a promiscuous envelope protein such as VSVg (Armentano, D. et al. (1987) J. Virol. 61:1647-1650; Bender, M.A. et al. (1987) J. Virol. 61:1639-1646; Adam, M.A. and 30 A.D. Miller (1988) J. Virol. 62:3802-3806; Dull, T. et al. (1998) J. Virol. 72:8463-8471; Zufferey, R. et al. (1998) J. Virol. 72:9873-9880). U.S. Patent No. 5,910,434 to Rigg ("Method for obtaining retrovirus packaging cell lines producing high transducing efficiency retroviral supernatant") discloses a method for obtaining retrovirus packaging cell lines and is hereby incorporated by reference. Propagation of retrovirus vectors, transduction of a population of cells (e.g., CD4<sup>+</sup> T- 35 cells), and the return of transduced cells to a patient are procedures well known to persons skilled in

the art of gene therapy and have been well documented (Ranga, U. et al. (1997) J. Virol. 71:7020-7029; Bauer, G. et al. (1997) Blood 89:2259-2267; Bonyhadi, M.L. (1997) J. Virol. 71:4707-4716; Ranga, U. et al. (1998) Proc. Natl. Acad. Sci. USA 95:1201-1206; Su, L. (1997) Blood 89:2283-2290).

5 In the alternative, an adenovirus-based gene therapy delivery system is used to deliver polynucleotides encoding KAP to cells which have one or more genetic abnormalities with respect to the expression of KAP. The construction and packaging of adenovirus-based vectors are well known to those with ordinary skill in the art. Replication defective adenovirus vectors have proven to be versatile for importing genes encoding immunoregulatory proteins into intact islets in the  
10 pancreas (Csete, M.E. et al. (1995) Transplantation 27:263-268). Potentially useful adenoviral vectors are described in U.S. Patent No. 5,707,618 to Armentano ("Adenovirus vectors for gene therapy"), hereby incorporated by reference. For adenoviral vectors, see also Antinozzi, P.A. et al. (1999) Annu. Rev. Nutr. 19:511-544 and Verma, I.M. and N. Somia (1997) Nature 18:389:239-242, both incorporated by reference herein.

15 In another alternative, a herpes-based, gene therapy delivery system is used to deliver polynucleotides encoding KAP to target cells which have one or more genetic abnormalities with respect to the expression of KAP. The use of herpes simplex virus (HSV)-based vectors may be especially valuable for introducing KAP to cells of the central nervous system, for which HSV has a tropism. The construction and packaging of herpes-based vectors are well known to those with  
20 ordinary skill in the art. A replication-competent herpes simplex virus (HSV) type 1-based vector has been used to deliver a reporter gene to the eyes of primates (Liu, X. et al. (1999) Exp. Eye Res. 169:385-395). The construction of a HSV-1 virus vector has also been disclosed in detail in U.S. Patent No. 5,804,413 to DeLuca ("Herpes simplex virus strains for gene transfer"), which is hereby incorporated by reference. U.S. Patent No. 5,804,413 teaches the use of recombinant HSV d92  
25 which consists of a genome containing at least one exogenous gene to be transferred to a cell under the control of the appropriate promoter for purposes including human gene therapy. Also taught by this patent are the construction and use of recombinant HSV strains deleted for ICP4, ICP27 and ICP22. For HSV vectors, see also Goins, W.F. et al. (1999) J. Virol. 73:519-532 and Xu, H. et al. (1994) Dev. Biol. 163:152-161, hereby incorporated by reference. The manipulation of cloned  
30 herpesvirus sequences, the generation of recombinant virus following the transfection of multiple plasmids containing different segments of the large herpesvirus genomes, the growth and propagation of herpesvirus, and the infection of cells with herpesvirus are techniques well known to those of ordinary skill in the art.

In another alternative, an alphavirus (positive, single-stranded RNA virus) vector is used to  
35 deliver polynucleotides encoding KAP to target cells. The biology of the prototypic alphavirus,

Semliki Forest Virus (SFV), has been studied extensively and gene transfer vectors have been based on the SFV genome (Garoff, H. and K.-J. Li (1998) Curr. Opin. Biotechnol. 9:464-469). During alphavirus RNA replication, a subgenomic RNA is generated that normally encodes the viral capsid proteins. This subgenomic RNA replicates to higher levels than the full length genomic RNA, resulting in the overproduction of capsid proteins relative to the viral proteins with enzymatic activity (e.g., protease and polymerase). Similarly, inserting the coding sequence for KAP into the alphavirus genome in place of the capsid-coding region results in the production of a large number of KAP-coding RNAs and the synthesis of high levels of KAP in vector transduced cells. While alphavirus infection is typically associated with cell lysis within a few days, the ability to establish a persistent infection in hamster normal kidney cells (BHK-21) with a variant of Sindbis virus (SIN) indicates that the lytic replication of alphaviruses can be altered to suit the needs of the gene therapy application (Dryga, S.A. et al. (1997) Virology 228:74-83). The wide host range of alphaviruses will allow the introduction of KAP into a variety of cell types. The specific transduction of a subset of cells in a population may require the sorting of cells prior to transduction. The methods of manipulating infectious cDNA clones of alphaviruses, performing alphavirus cDNA and RNA transfections, and performing alphavirus infections, are well known to those with ordinary skill in the art.

Oligonucleotides derived from the transcription initiation site, e.g., between about positions -10 and +10 from the start site, may also be employed to inhibit gene expression. Similarly, inhibition can be achieved using triple helix base-pairing methodology. Triple helix pairing is useful because it causes inhibition of the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors, or regulatory molecules. Recent therapeutic advances using triplex DNA have been described in the literature. (See, e.g., Gee, J.E. et al. (1994) in Huber, B.E. and B.I. Carr, Molecular and Immunologic Approaches, Futura Publishing, Mt. Kisco NY, pp. 163-177.) A complementary sequence or antisense molecule may also be designed to block translation of mRNA by preventing the transcript from binding to ribosomes.

Ribozymes, enzymatic RNA molecules, may also be used to catalyze the specific cleavage of RNA. The mechanism of ribozyme action involves sequence-specific hybridization of the ribozyme molecule to complementary target RNA, followed by endonucleolytic cleavage. For example, engineered hammerhead motif ribozyme molecules may specifically and efficiently catalyze endonucleolytic cleavage of sequences encoding KAP.

Specific ribozyme cleavage sites within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites, including the following sequences: GUA, GUU, and GUC. Once identified, short RNA sequences of between 15 and 20 ribonucleotides, corresponding to the region of the target gene containing the cleavage site, may be evaluated for

secondary structural features which may render the oligonucleotide inoperable. The suitability of candidate targets may also be evaluated by testing accessibility to hybridization with complementary oligonucleotides using ribonuclease protection assays.

Complementary ribonucleic acid molecules and ribozymes of the invention may be prepared 5 by any method known in the art for the synthesis of nucleic acid molecules. These include techniques for chemically synthesizing oligonucleotides such as solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by in vitro and in vivo transcription of DNA sequences encoding KAP. Such DNA sequences may be incorporated into a wide variety of vectors with suitable RNA polymerase promoters such as T7 or SP6. Alternatively, 10 these cDNA constructs that synthesize complementary RNA, constitutively or inducibly, can be introduced into cell lines, cells, or tissues.

RNA molecules may be modified to increase intracellular stability and half-life. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends of the molecule, or the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase 15 linkages within the backbone of the molecule. This concept is inherent in the production of PNAs and can be extended in all of these molecules by the inclusion of nontraditional bases such as inosine, queosine, and wybutosine, as well as acetyl-, methyl-, thio-, and similarly modified forms of adenine, cytidine, guanine, thymine, and uridine which are not as easily recognized by endogenous endonucleases.

20 An additional embodiment of the invention encompasses a method for screening for a compound which is effective in altering expression of a polynucleotide encoding KAP. Compounds which may be effective in altering expression of a specific polynucleotide may include, but are not limited to, oligonucleotides, antisense oligonucleotides, triple helix-forming oligonucleotides, transcription factors and other polypeptide transcriptional regulators, and non-macromolecular 25 chemical entities which are capable of interacting with specific polynucleotide sequences. Effective compounds may alter polynucleotide expression by acting as either inhibitors or promoters of polynucleotide expression. Thus, in the treatment of disorders associated with increased KAP expression or activity, a compound which specifically inhibits expression of the polynucleotide encoding KAP may be therapeutically useful, and in the treatment of disorders associated with 30 decreased KAP expression or activity, a compound which specifically promotes expression of the polynucleotide encoding KAP may be therapeutically useful.

At least one, and up to a plurality, of test compounds may be screened for effectiveness in altering expression of a specific polynucleotide. A test compound may be obtained by any method commonly known in the art, including chemical modification of a compound known to be effective 35 in altering polynucleotide expression; selection from an existing, commercially-available or

proprietary library of naturally-occurring or non-natural chemical compounds; rational design of a compound based on chemical and/or structural properties of the target polynucleotide; and selection from a library of chemical compounds created combinatorially or randomly. A sample comprising a polynucleotide encoding KAP is exposed to at least one test compound thus obtained. The sample  
5 may comprise, for example, an intact or permeabilized cell, or an in vitro cell-free or reconstituted biochemical system. Alterations in the expression of a polynucleotide encoding KAP are assayed by any method commonly known in the art. Typically, the expression of a specific nucleotide is detected by hybridization with a probe having a nucleotide sequence complementary to the sequence of the polynucleotide encoding KAP. The amount of hybridization may be quantified,  
10 thus forming the basis for a comparison of the expression of the polynucleotide both with and without exposure to one or more test compounds. Detection of a change in the expression of a polynucleotide exposed to a test compound indicates that the test compound is effective in altering the expression of the polynucleotide. A screen for a compound effective in altering expression of a specific polynucleotide can be carried out, for example, using a Schizosaccharomyces pombe gene  
15 expression system (Atkins, D. et al. (1999) U.S. Patent No. 5,932,435; Arndt, G.M. et al. (2000) Nucleic Acids Res. 28:E15) or a human cell line such as HeLa cell (Clarke, M.L. et al. (2000) Biochem. Biophys. Res. Commun. 268:8-13). A particular embodiment of the present invention involves screening a combinatorial library of oligonucleotides (such as deoxyribonucleotides, ribonucleotides, peptide nucleic acids, and modified oligonucleotides) for antisense activity against  
20 a specific polynucleotide sequence (Bruce, T.W. et al. (1997) U.S. Patent No. 5,686,242; Bruce, T.W. et al. (2000) U.S. Patent No. 6,022,691).

Many methods for introducing vectors into cells or tissues are available and equally suitable for use in vivo, in vitro, and ex vivo. For ex vivo therapy, vectors may be introduced into stem cells taken from the patient and clonally propagated for autologous transplant back into that same patient.  
25 Delivery by transfection, by liposome injections, or by polycationic amino polymers may be achieved using methods which are well known in the art. (See, e.g., Goldman, C.K. et al. (1997) Nat. Biotechnol. 15:462-466.)

Any of the therapeutic methods described above may be applied to any subject in need of such therapy, including, for example, mammals such as humans, dogs, cats, cows, horses, rabbits,  
30 and monkeys.

An additional embodiment of the invention relates to the administration of a composition which generally comprises an active ingredient formulated with a pharmaceutically acceptable excipient. Excipients may include, for example, sugars, starches, celluloses, gums, and proteins. Various formulations are commonly known and are thoroughly discussed in the latest edition of  
35 Remington's Pharmaceutical Sciences (Maack Publishing, Easton PA). Such compositions may

consist of KAP, antibodies to KAP, and mimetics, agonists, antagonists, or inhibitors of KAP.

The compositions utilized in this invention may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, pulmonary, transdermal, subcutaneous, intraperitoneal, intranasal, 5 enteral, topical, sublingual, or rectal means.

Compositions for pulmonary administration may be prepared in liquid or dry powder form. These compositions are generally aerosolized immediately prior to inhalation by the patient. In the case of small molecules (e.g. traditional low molecular weight organic drugs), aerosol delivery of fast-acting formulations is well-known in the art. In the case of macromolecules (e.g. larger 10 peptides and proteins), recent developments in the field of pulmonary delivery via the alveolar region of the lung have enabled the practical delivery of drugs such as insulin to blood circulation (see, e.g., Patton, J.S. et al., U.S. Patent No. 5,997,848). Pulmonary delivery has the advantage of administration without needle injection, and obviates the need for potentially toxic penetration enhancers.

15 Compositions suitable for use in the invention include compositions wherein the active ingredients are contained in an effective amount to achieve the intended purpose. The determination of an effective dose is well within the capability of those skilled in the art.

Specialized forms of compositions may be prepared for direct intracellular delivery of macromolecules comprising KAP or fragments thereof. For example, liposome preparations 20 containing a cell-impermeable macromolecule may promote cell fusion and intracellular delivery of the macromolecule. Alternatively, KAP or a fragment thereof may be joined to a short cationic N-terminal portion from the HIV Tat-1 protein. Fusion proteins thus generated have been found to transduce into the cells of all tissues, including the brain, in a mouse model system (Schwarze, S.R. et al. (1999) Science 285:1569-1572).

25 For any compound, the therapeutically effective dose can be estimated initially either in cell culture assays, e.g., of neoplastic cells, or in animal models such as mice, rats, rabbits, dogs, monkeys, or pigs. An animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans.

30 A therapeutically effective dose refers to that amount of active ingredient, for example KAP or fragments thereof, antibodies of KAP, and agonists, antagonists or inhibitors of KAP, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such as by calculating the ED<sub>50</sub> (the dose therapeutically effective in 50% of the population) or LD<sub>50</sub> (the dose 35 lethal to 50% of the population) statistics. The dose ratio of toxic to therapeutic effects is the

therapeutic index, which can be expressed as the  $LD_{50}/ED_{50}$  ratio. Compositions which exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies are used to formulate a range of dosage for human use. The dosage contained in such compositions is preferably within a range of circulating concentrations that includes the  $ED_{50}$  with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, the sensitivity of the patient, and the route of administration.

The exact dosage will be determined by the practitioner, in light of factors related to the subject requiring treatment. Dosage and administration are adjusted to provide sufficient levels of the active moiety or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, the general health of the subject, the age, weight, and gender of the subject, time and frequency of administration, drug combination(s), reaction sensitivities, and response to therapy. Long-acting compositions may be administered every 3 to 4 days, every week, or biweekly depending on the half-life and clearance rate of the particular formulation.

Normal dosage amounts may vary from about  $0.1 \mu\text{g}$  to  $100,000 \mu\text{g}$ , up to a total dose of about 1 gram, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art. Those skilled in the art will employ different formulations for nucleotides than for proteins or their inhibitors. Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells, conditions, locations, etc.

## 20 DIAGNOSTICS

In another embodiment, antibodies which specifically bind KAP may be used for the diagnosis of disorders characterized by expression of KAP, or in assays to monitor patients being treated with KAP or agonists, antagonists, or inhibitors of KAP. Antibodies useful for diagnostic purposes may be prepared in the same manner as described above for therapeutics. Diagnostic assays for KAP include methods which utilize the antibody and a label to detect KAP in human body fluids or in extracts of cells or tissues. The antibodies may be used with or without modification, and may be labeled by covalent or non-covalent attachment of a reporter molecule. A wide variety of reporter molecules, several of which are described above, are known in the art and may be used.

A variety of protocols for measuring KAP, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of KAP expression. Normal or standard values for KAP expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, for example, human subjects, with antibodies to KAP under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, such as photometric means. Quantities of KAP expressed in



subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease.

In another embodiment of the invention, the polynucleotides encoding KAP may be used for diagnostic purposes. The polynucleotides which may be used include oligonucleotide sequences, 5 complementary RNA and DNA molecules, and PNAs. The polynucleotides may be used to detect and quantify gene expression in biopsied tissues in which expression of KAP may be correlated with disease. The diagnostic assay may be used to determine absence, presence, and excess expression of KAP, and to monitor regulation of KAP levels during therapeutic intervention.

In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide 10 sequences, including genomic sequences, encoding KAP or closely related molecules may be used to identify nucleic acid sequences which encode KAP. The specificity of the probe, whether it is made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a conserved motif, and the stringency of the hybridization or amplification will determine whether the probe identifies only naturally occurring sequences encoding KAP, allelic variants, or related 15 sequences.

Probes may also be used for the detection of related sequences, and may have at least 50% sequence identity to any of the KAP encoding sequences. The hybridization probes of the subject invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:21-40 or from genomic sequences including promoters, enhancers, and introns of the KAP gene.

20 Means for producing specific hybridization probes for DNAs encoding KAP include the cloning of polynucleotide sequences encoding KAP or KAP derivatives into vectors for the production of mRNA probes. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by means of the addition of the appropriate RNA polymerases and the appropriate labeled nucleotides. Hybridization probes may be labeled by a 25 variety of reporter groups, for example, by radionuclides such as  $^{32}\text{P}$  or  $^{35}\text{S}$ , or by enzymatic labels, such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems, and the like.

Polynucleotide sequences encoding KAP may be used for the diagnosis of disorders associated with expression of KAP. Examples of such disorders include, but are not limited to, a cardiovascular disorder such as arteriovenous fistula, atherosclerosis, hypertension, vasculitis, 30 Raynaud's disease, aneurysms, arterial dissections, varicose veins, thrombophlebitis and phlebothrombosis, vascular tumors, and complications of thrombolysis, balloon angioplasty, vascular replacement, and coronary artery bypass graft surgery, congestive heart failure, ischemic heart disease, angina pectoris, myocardial infarction, hypertensive heart disease, degenerative valvular heart disease, calcific aortic valve stenosis, congenitally bicuspid aortic valve, mitral 35 annular calcification, mitral valve prolapse, rheumatic fever and rheumatic heart disease, infective

endocarditis, nonbacterial thrombotic endocarditis, endocarditis of systemic lupus erythematosus, carcinoid heart disease, cardiomyopathy, myocarditis, pericarditis, neoplastic heart disease, congenital heart disease, and complications of cardiac transplantation, congenital lung anomalies, atelectasis, pulmonary congestion and edema, pulmonary embolism, pulmonary hemorrhage,

5 pulmonary infarction, pulmonary hypertension, vascular sclerosis, obstructive pulmonary disease, restrictive pulmonary disease, chronic obstructive pulmonary disease, emphysema, chronic bronchitis, bronchial asthma, bronchiectasis, bacterial pneumonia, viral and mycoplasmal pneumonia, lung abscess, pulmonary tuberculosis, diffuse interstitial diseases, pneumoconioses, sarcoidosis, idiopathic pulmonary fibrosis, desquamative interstitial pneumonitis, hypersensitivity

10 pneumonitis, pulmonary eosinophilia bronchiolitis obliterans-organizing pneumonia, diffuse pulmonary hemorrhage syndromes, Goodpasture's syndromes, idiopathic pulmonary hemosiderosis, pulmonary involvement in collagen-vascular disorders, pulmonary alveolar proteinosis, lung tumors, inflammatory and noninflammatory pleural effusions, pneumothorax, pleural tumors, drug-induced lung disease, radiation-induced lung disease, and complications of lung transplantation; an immune

15 disorder such as acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia

20 with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic

25 lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, and trauma; a neurological disorder such as epilepsy, ischemic cerebrovascular disease, stroke, cerebral neoplasms, Alzheimer's disease, Pick's disease, Huntington's disease, dementia, Parkinson's disease and other

30 extrapyramidal disorders, amyotrophic lateral sclerosis and other motor neuron disorders, progressive neural muscular atrophy, retinitis pigmentosa, hereditary ataxias, multiple sclerosis and other demyelinating diseases, bacterial and viral meningitis, brain abscess, subdural empyema, epidural abscess, suppurative intracranial thrombophlebitis, myelitis and radiculitis, viral central nervous system disease, prion diseases including kuru, Creutzfeldt-Jakob disease, and Gerstmann-

35 Straussler-Scheinker syndrome, fatal familial insomnia, nutritional and metabolic diseases of the

nervous system, neurofibromatosis, tuberous sclerosis, cerebelloretinal hemangioblastomatosis, encephalotrigeminal syndrome, mental retardation and other developmental disorders of the central nervous system including Down syndrome, cerebral palsy, neuroskeletal disorders, autonomic nervous system disorders, cranial nerve disorders, spinal cord diseases, muscular dystrophy and  
 5 other neuromuscular disorders, peripheral nervous system disorders, dermatomyositis and polymyositis, inherited, metabolic, endocrine, and toxic myopathies, myasthenia gravis, periodic paralysis, mental disorders including mood, anxiety, and schizophrenic disorders, seasonal affective disorder (SAD), akathisia, amnesia, catatonia, diabetic neuropathy, tardive dyskinesia, dystonias, paranoid psychoses, postherpetic neuralgia, Tourette's disorder, progressive supranuclear palsy,  
 10 corticobasal degeneration, and familial frontotemporal dementia; a growth and developmental disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, renal tubular acidosis, anemia, Cushing's syndrome, achondroplastic dwarfism, Duchenne and Becker muscular dystrophy, epilepsy, gonadal  
 15 dysgenesis, WAGR syndrome (Wilms' tumor, aniridia, genitourinary abnormalities, and mental retardation), Smith-Magenis syndrome, myelodysplastic syndrome, hereditary mucoepithelial dysplasia, hereditary keratodermas, hereditary neuropathies such as Charcot-Marie-Tooth disease and neurofibromatosis, hypothyroidism, hydrocephalus, seizure disorders such as Sydenham's chorea and cerebral palsy, spina bifida, anencephaly, craniorachischisis, congenital glaucoma,  
 20 cataract, and sensorineural hearing loss; a lipid disorder such as fatty liver, cholestasis, primary biliary cirrhosis, carnitine deficiency, carnitine palmitoyltransferase deficiency, myoadenylate deaminase deficiency, hypertriglyceridemia, lipid storage disorders such as Fabry's disease, Gaucher's disease, Niemann-Pick's disease, metachromatic leukodystrophy, adrenoleukodystrophy, GM<sub>2</sub> gangliosidosis, and ceroid lipofuscinosis, abetalipoproteinemia, Tangier disease,  
 25 hyperlipoproteinemia, diabetes mellitus, lipodystrophy, lipomatoses, acute panniculitis, disseminated fat necrosis, adiposis dolorosa, lipoid adrenal hyperplasia, minimal change disease, lipomas, atherosclerosis, hypercholesterolemia, hypercholesterolemia with hypertriglyceridemia, primary hypoalphalipoproteinemia, hypothyroidism, renal disease, liver disease, lecithin:cholesterol acyltransferase deficiency, cerebrotendinous xanthomatosis, sitosterolemia, hypocholesterolemia,  
 30 Tay-Sachs disease, Sandhoff's disease, hyperlipidemia, hyperlipemia, lipid myopathies, and obesity; and a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma,  
 35 and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix,

gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, uterus, leukemias such as multiple myeloma, and lymphomas such as Hodgkin's disease. The polynucleotide sequences encoding KAP may be used in Southern or northern analysis, dot blot, or other  
5 membrane-based technologies; in PCR technologies; in dipstick, pin, and multiformat ELISA-like assays; and in microarrays utilizing fluids or tissues from patients to detect altered KAP expression. Such qualitative or quantitative methods are well known in the art.

In a particular aspect, the nucleotide sequences encoding KAP may be useful in assays that detect the presence of associated disorders, particularly those mentioned above. The nucleotide  
10 sequences encoding KAP may be labeled by standard methods and added to a fluid or tissue sample from a patient under conditions suitable for the formation of hybridization complexes. After a suitable incubation period, the sample is washed and the signal is quantified and compared with a standard value. If the amount of signal in the patient sample is significantly altered in comparison to a control sample then the presence of altered levels of nucleotide sequences encoding KAP in the  
15 sample indicates the presence of the associated disorder. Such assays may also be used to evaluate the efficacy of a particular therapeutic treatment regimen in animal studies, in clinical trials, or to monitor the treatment of an individual patient.

In order to provide a basis for the diagnosis of a disorder associated with expression of KAP, a normal or standard profile for expression is established. This may be accomplished by  
20 combining body fluids or cell extracts taken from normal subjects, either animal or human, with a sequence, or a fragment thereof, encoding KAP, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by comparing the values obtained from normal subjects with values from an experiment in which a known amount of a substantially purified polynucleotide is used. Standard values obtained in this manner may be compared with  
25 values obtained from samples from patients who are symptomatic for a disorder. Deviation from standard values is used to establish the presence of a disorder.

Once the presence of a disorder is established and a treatment protocol is initiated, hybridization assays may be repeated on a regular basis to determine if the level of expression in the patient begins to approximate that which is observed in the normal subject. The results obtained  
30 from successive assays may be used to show the efficacy of treatment over a period ranging from several days to months.

With respect to cancer, the presence of an abnormal amount of transcript (either under- or overexpressed) in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the  
35 appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health

professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Additional diagnostic uses for oligonucleotides designed from the sequences encoding KAP may involve the use of PCR. These oligomers may be chemically synthesized, generated 5 enzymatically, or produced in vitro. Oligomers will preferably contain a fragment of a polynucleotide encoding KAP, or a fragment of a polynucleotide complementary to the polynucleotide encoding KAP, and will be employed under optimized conditions for identification of a specific gene or condition. Oligomers may also be employed under less stringent conditions for detection or quantification of closely related DNA or RNA sequences.

10 In a particular aspect, oligonucleotide primers derived from the polynucleotide sequences encoding KAP may be used to detect single nucleotide polymorphisms (SNPs). SNPs are substitutions, insertions and deletions that are a frequent cause of inherited or acquired genetic disease in humans. Methods of SNP detection include, but are not limited to, single-stranded conformation polymorphism (SSCP) and fluorescent SSCP (fSSCP) methods. In SSCP, 15 oligonucleotide primers derived from the polynucleotide sequences encoding KAP are used to amplify DNA using the polymerase chain reaction (PCR). The DNA may be derived, for example, from diseased or normal tissue, biopsy samples, bodily fluids, and the like. SNPs in the DNA cause differences in the secondary and tertiary structures of PCR products in single-stranded form, and these differences are detectable using gel electrophoresis in non-denaturing gels. In fSSCP, the 20 oligonucleotide primers are fluorescently labeled, which allows detection of the amplimers in high-throughput equipment such as DNA sequencing machines. Additionally, sequence database analysis methods, termed *in silico* SNP (isSNP), are capable of identifying polymorphisms by comparing the sequence of individual overlapping DNA fragments which assemble into a common consensus sequence. These computer-based methods filter out sequence variations due to 25 laboratory preparation of DNA and sequencing errors using statistical models and automated analyses of DNA sequence chromatograms. In the alternative, SNPs may be detected and characterized by mass spectrometry using, for example, the high throughput MASSARRAY system (Sequenom, Inc., San Diego CA).

Methods which may also be used to quantify the expression of KAP include radiolabeling 30 or biotinylating nucleotides, coamplification of a control nucleic acid, and interpolating results from standard curves. (See, e.g., Melby, P.C. et al. (1993) J. Immunol. Methods 159:235-244; Duplaa, C. et al. (1993) Anal. Biochem. 212:229-236.) The speed of quantitation of multiple samples may be accelerated by running the assay in a high-throughput format where the oligomer or polynucleotide of interest is presented in various dilutions and a spectrophotometric or colorimetric response gives 35 rapid quantitation.

In further embodiments, oligonucleotides or longer fragments derived from any of the polynucleotide sequences described herein may be used as elements on a microarray. The microarray can be used in transcript imaging techniques which monitor the relative expression levels of large numbers of genes simultaneously as described below. The microarray may also be used to identify genetic variants, mutations, and polymorphisms. This information may be used to determine gene function, to understand the genetic basis of a disorder, to diagnose a disorder, to monitor progression/regression of disease as a function of gene expression, and to develop and monitor the activities of therapeutic agents in the treatment of disease. In particular, this information may be used to develop a pharmacogenomic profile of a patient in order to select the most appropriate and effective treatment regimen for that patient. For example, therapeutic agents which are highly effective and display the fewest side effects may be selected for a patient based on his/her pharmacogenomic profile.

In another embodiment, KAP, fragments of KAP, or antibodies specific for KAP may be used as elements on a microarray. The microarray may be used to monitor or measure protein-protein interactions, drug-target interactions, and gene expression profiles, as described above.

A particular embodiment relates to the use of the polynucleotides of the present invention to generate a transcript image of a tissue or cell type. A transcript image represents the global pattern of gene expression by a particular tissue or cell type. Global gene expression patterns are analyzed by quantifying the number of expressed genes and their relative abundance under given conditions and at a given time. (See Seilhamer et al., "Comparative Gene Transcript Analysis," U.S. Patent No. 5,840,484, expressly incorporated by reference herein.) Thus a transcript image may be generated by hybridizing the polynucleotides of the present invention or their complements to the totality of transcripts or reverse transcripts of a particular tissue or cell type. In one embodiment, the hybridization takes place in high-throughput format, wherein the polynucleotides of the present invention or their complements comprise a subset of a plurality of elements on a microarray. The resultant transcript image would provide a profile of gene activity.

Transcript images may be generated using transcripts isolated from tissues, cell lines, biopsies, or other biological samples. The transcript image may thus reflect gene expression in vivo, as in the case of a tissue or biopsy sample, or in vitro, as in the case of a cell line.

Transcript images which profile the expression of the polynucleotides of the present invention may also be used in conjunction with in vitro model systems and preclinical evaluation of pharmaceuticals, as well as toxicological testing of industrial and naturally-occurring environmental compounds. All compounds induce characteristic gene expression patterns, frequently termed molecular fingerprints or toxicant signatures, which are indicative of mechanisms of action and toxicity (Nuwaysir, E.F. et al. (1999) Mol. Carcinog. 24:153-159; Steiner, S. and N.L. Anderson

(2000) Toxicol. Lett. 112-113:467-471, expressly incorporated by reference herein). If a test compound has a signature similar to that of a compound with known toxicity, it is likely to share those toxic properties. These fingerprints or signatures are most useful and refined when they contain expression information from a large number of genes and gene families. Ideally, a genome-wide measurement of expression provides the highest quality signature. Even genes whose expression is not altered by any tested compounds are important as well, as the levels of expression of these genes are used to normalize the rest of the expression data. The normalization procedure is useful for comparison of expression data after treatment with different compounds. While the assignment of gene function to elements of a toxicant signature aids in interpretation of toxicity mechanisms, knowledge of gene function is not necessary for the statistical matching of signatures which leads to prediction of toxicity. (See, for example, Press Release 00-02 from the National Institute of Environmental Health Sciences, released February 29, 2000, available at <http://www.niehs.nih.gov/oc/news/toxchip.htm>.) Therefore, it is important and desirable in toxicological screening using toxicant signatures to include all expressed gene sequences.

15 In one embodiment, the toxicity of a test compound is assessed by treating a biological sample containing nucleic acids with the test compound. Nucleic acids that are expressed in the treated biological sample are hybridized with one or more probes specific to the polynucleotides of the present invention, so that transcript levels corresponding to the polynucleotides of the present invention may be quantified. The transcript levels in the treated biological sample are compared with levels in an untreated biological sample. Differences in the transcript levels between the two samples are indicative of a toxic response caused by the test compound in the treated sample.

Another particular embodiment relates to the use of the polypeptide sequences of the present invention to analyze the proteome of a tissue or cell type. The term proteome refers to the global pattern of protein expression in a particular tissue or cell type. Each protein component of a proteome can be subjected individually to further analysis. Proteome expression patterns, or profiles, are analyzed by quantifying the number of expressed proteins and their relative abundance under given conditions and at a given time. A profile of a cell's proteome may thus be generated by separating and analyzing the polypeptides of a particular tissue or cell type. In one embodiment, the separation is achieved using two-dimensional gel electrophoresis, in which proteins from a sample are separated by isoelectric focusing in the first dimension, and then according to molecular weight by sodium dodecyl sulfate slab gel electrophoresis in the second dimension (Steiner and Anderson, supra). The proteins are visualized in the gel as discrete and uniquely positioned spots, typically by staining the gel with an agent such as Coomassie Blue or silver or fluorescent stains. The optical density of each protein spot is generally proportional to the level of the protein in the sample. The optical densities of equivalently positioned protein spots from different samples, for example, from

biological samples either treated or untreated with a test compound or therapeutic agent, are compared to identify any changes in protein spot density related to the treatment. The proteins in the spots are partially sequenced using, for example, standard methods employing chemical or enzymatic cleavage followed by mass spectrometry. The identity of the protein in a spot may be determined by comparing its partial sequence, preferably of at least 5 contiguous amino acid residues, to the polypeptide sequences of the present invention. In some cases, further sequence data may be obtained for definitive protein identification.

A proteomic profile may also be generated using antibodies specific for KAP to quantify the levels of KAP expression. In one embodiment, the antibodies are used as elements on a microarray, and protein expression levels are quantified by exposing the microarray to the sample and detecting the levels of protein bound to each array element (Lueking, A. et al. (1999) *Anal. Biochem.* 270:103-111; Mendoz, L.G. et al. (1999) *Biotechniques* 27:778-788). Detection may be performed by a variety of methods known in the art, for example, by reacting the proteins in the sample with a thiol- or amino-reactive fluorescent compound and detecting the amount of fluorescence bound at 15 each array element.

Toxicant signatures at the proteome level are also useful for toxicological screening, and should be analyzed in parallel with toxicant signatures at the transcript level. There is a poor correlation between transcript and protein abundances for some proteins in some tissues (Anderson, N.L. and J. Seilhamer (1997) *Electrophoresis* 18:533-537), so proteome toxicant signatures may be useful in the analysis of compounds which do not significantly affect the transcript image, but which alter the proteomic profile. In addition, the analysis of transcripts in body fluids is difficult, due to rapid degradation of mRNA, so proteomic profiling may be more reliable and informative in such cases.

In another embodiment, the toxicity of a test compound is assessed by treating a biological sample containing proteins with the test compound. Proteins that are expressed in the treated biological sample are separated so that the amount of each protein can be quantified. The amount of each protein is compared to the amount of the corresponding protein in an untreated biological sample. A difference in the amount of protein between the two samples is indicative of a toxic response to the test compound in the treated sample. Individual proteins are identified by sequencing the amino acid residues of the individual proteins and comparing these partial sequences to the polypeptides of the present invention.

In another embodiment, the toxicity of a test compound is assessed by treating a biological sample containing proteins with the test compound. Proteins from the biological sample are incubated with antibodies specific to the polypeptides of the present invention. The amount of protein recognized by the antibodies is quantified. The amount of protein in the treated biological



sample is compared with the amount in an untreated biological sample. A difference in the amount of protein between the two samples is indicative of a toxic response to the test compound in the treated sample.

Microarrays may be prepared, used, and analyzed using methods known in the art. (See, 5 e.g., Brennan, T.M. et al. (1995) U.S. Patent No. 5,474,796; Schena, M. et al. (1996) Proc. Natl. Acad. Sci. USA 93:10614-10619; Baldeschweiler et al. (1995) PCT application WO95/251116; Shalon, D. et al. (1995) PCT application WO95/35505; Heller, R.A. et al. (1997) Proc. Natl. Acad. Sci. USA 94:2150-2155; and Heller, M.J. et al. (1997) U.S. Patent No. 5,605,662.) Various types of microarrays are well known and thoroughly described in DNA Microarrays: A Practical Approach, 10 M. Schena, ed. (1999) Oxford University Press, London, hereby expressly incorporated by reference.

In another embodiment of the invention, nucleic acid sequences encoding KAP may be used to generate hybridization probes useful in mapping the naturally occurring genomic sequence. Either coding or noncoding sequences may be used, and in some instances, noncoding sequences 15 may be preferable over coding sequences. For example, conservation of a coding sequence among members of a multi-gene family may potentially cause undesired cross hybridization during chromosomal mapping. The sequences may be mapped to a particular chromosome, to a specific region of a chromosome, or to artificial chromosome constructions, e.g., human artificial chromosomes (HACs), yeast artificial chromosomes (YACs), bacterial artificial chromosomes 20 (BACs), bacterial P1 constructions, or single chromosome cDNA libraries. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355; Price, C.M. (1993) Blood Rev. 7:127-134; and Trask, B.J. (1991) Trends Genet. 7:149-154.) Once mapped, the nucleic acid sequences of the invention may be used to develop genetic linkage maps, for example, which correlate the inheritance of a disease state with the inheritance of a particular chromosome region or restriction fragment length 25 polymorphism (RFLP). (See, for example, Lander, E.S. and D. Botstein (1986) Proc. Natl. Acad. Sci. USA 83:7353-7357.)

Fluorescent in situ hybridization (FISH) may be correlated with other physical and genetic map data. (See, e.g., Heinz-Ulrich, et al. (1995) in Meyers, supra, pp. 965-968.) Examples of genetic map data can be found in various scientific journals or at the Online Mendelian Inheritance 30 in Man (OMIM) World Wide Web site. Correlation between the location of the gene encoding KAP on a physical map and a specific disorder, or a predisposition to a specific disorder, may help define the region of DNA associated with that disorder and thus may further positional cloning efforts.

In situ hybridization of chromosomal preparations and physical mapping techniques, such as 35 linkage analysis using established chromosomal markers, may be used for extending genetic maps.

Often the placement of a gene on the chromosome of another mammalian species, such as mouse, may reveal associated markers even if the exact chromosomal locus is not known. This information is valuable to investigators searching for disease genes using positional cloning or other gene discovery techniques. Once the gene or genes responsible for a disease or syndrome have been crudely localized by genetic linkage to a particular genomic region, e.g., ataxia-telangiectasia to 11q22-23, any sequences mapping to that area may represent associated or regulatory genes for further investigation. (See, e.g., Gatti, R.A. et al. (1988) *Nature* 336:577-580.) The nucleotide sequence of the instant invention may also be used to detect differences in the chromosomal location due to translocation, inversion, etc., among normal, carrier, or affected individuals.

10 In another embodiment of the invention, KAP, its catalytic or immunogenic fragments, or oligopeptides thereof can be used for screening libraries of compounds in any of a variety of drug screening techniques. The fragment employed in such screening may be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. The formation of binding complexes between KAP and the agent being tested may be measured.

15 Another technique for drug screening provides for high throughput screening of compounds having suitable binding affinity to the protein of interest. (See, e.g., Geysen, et al. (1984) PCT application WO84/03564.) In this method, large numbers of different small test compounds are synthesized on a solid substrate. The test compounds are reacted with KAP, or fragments thereof, and washed. Bound KAP is then detected by methods well known in the art. Purified KAP can also be coated directly onto plates for use in the aforementioned drug screening techniques.

Alternatively, non-neutralizing antibodies can be used to capture the peptide and immobilize it on a solid support.

In another embodiment, one may use competitive drug screening assays in which neutralizing antibodies capable of binding KAP specifically compete with a test compound for binding KAP. In this manner, antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with KAP.

In additional embodiments, the nucleotide sequences which encode KAP may be used in any molecular biology techniques that have yet to be developed, provided the new techniques rely on properties of nucleotide sequences that are currently known, including, but not limited to, such properties as the triplet genetic code and specific base pair interactions.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

35 The disclosures of all patents, applications and publications, mentioned above and below,

including U.S. Ser. No. 60/254,034, U.S. Ser. No. 60/255,756, U.S. Ser. No. 60/251,814, U.S. Ser. No. 60/256,172, U.S. Ser. No. 60/257,416, U.S. Ser. No. 60/260,912, U.S. Ser. No. 60/264,344, and U.S. Ser. No. 60/266,017, are expressly incorporated by reference herein.

5

## EXAMPLES

### I. Construction of cDNA Libraries

Incyte cDNAs were derived from cDNA libraries described in the LIFESEQ GOLD database (Incyte Genomics, Palo Alto CA). Some tissues were homogenized and lysed in guanidinium isothiocyanate, while others were homogenized and lysed in phenol or in a suitable mixture of denaturants, such as TRIZOL (Life Technologies), a monophasic solution of phenol and guanidine isothiocyanate. The resulting lysates were centrifuged over CsCl cushions or extracted with chloroform. RNA was precipitated from the lysates with either isopropanol or sodium acetate and ethanol, or by other routine methods.

Phenol extraction and precipitation of RNA were repeated as necessary to increase RNA purity. In some cases, RNA was treated with DNase. For most libraries, poly(A)+ RNA was isolated using oligo d(T)-coupled paramagnetic particles (Promega), OLIGOTEX latex particles (QIAGEN, Chatsworth CA), or an OLIGOTEX mRNA purification kit (QIAGEN). Alternatively, RNA was isolated directly from tissue lysates using other RNA isolation kits, e.g., the POLY(A)PURE mRNA purification kit (Ambion, Austin TX).

In some cases, Stratagene was provided with RNA and constructed the corresponding cDNA libraries. Otherwise, cDNA was synthesized and cDNA libraries were constructed with the UNIZAP vector system (Stratagene) or SUPERScript plasmid system (Life Technologies), using the recommended procedures or similar methods known in the art. (See, e.g., Ausubel, 1997, *supra*, units 5.1-6.6.) Reverse transcription was initiated using oligo d(T) or random primers. Synthetic oligonucleotide adapters were ligated to double stranded cDNA, and the cDNA was digested with the appropriate restriction enzyme or enzymes. For most libraries, the cDNA was size-selected (300-1000 bp) using SEPHACRYL S1000, SEPHAROSE CL2B, or SEPHAROSE CL4B column chromatography (Amersham Pharmacia Biotech) or preparative agarose gel electrophoresis. cDNAs were ligated into compatible restriction enzyme sites of the polylinker of a suitable plasmid, e.g., PBLUESCRIPT plasmid (Stratagene), PSPORT1 plasmid (Life Technologies), PCDNA2.1 plasmid (Invitrogen, Carlsbad CA), PBK-CMV plasmid (Stratagene), PCR2-TOPOTA plasmid (Invitrogen), PCMV-ICIS plasmid (Stratagene), pIGEN (Incyte Genomics, Palo Alto CA), pRARE (Incyte Genomics), or pINCY (Incyte Genomics), or derivatives thereof. Recombinant plasmids were transformed into competent *E. coli* cells including XL1-Blue, XL1-BlueMRF, or SOLR from 35 Stratagene or DH5 $\alpha$ , DH10B, or ElectroMAX DH10B from Life Technologies.

## II. Isolation of cDNA Clones

Plasmids obtained as described in Example I were recovered from host cells by in vivo excision using the UNIZAP vector system (Stratagene) or by cell lysis. Plasmids were purified using at least one of the following: a Magic or WIZARD Minipreps DNA purification system (Promega); an AGTC Miniprep purification kit (Edge Biosystems, Gaithersburg MD); and QIAWELL 8 Plasmid, QIAWELL 8 Plus Plasmid, QIAWELL 8 Ultra Plasmid purification systems or the R.E.A.L. PREP 96 plasmid purification kit from QIAGEN. Following precipitation, plasmids were resuspended in 0.1 ml of distilled water and stored, with or without lyophilization, at 4°C.

Alternatively, plasmid DNA was amplified from host cell lysates using direct link PCR in a high-throughput format (Rao, V.B. (1994) Anal. Biochem. 216:1-14). Host cell lysis and thermal cycling steps were carried out in a single reaction mixture. Samples were processed and stored in 384-well plates, and the concentration of amplified plasmid DNA was quantified fluorometrically using PICOGREEN dye (Molecular Probes, Eugene OR) and a FLUOROSKAN II fluorescence scanner (Labsystems Oy, Helsinki, Finland).

## 15 III. Sequencing and Analysis

Incyte cDNA recovered in plasmids as described in Example II were sequenced as follows. Sequencing reactions were processed using standard methods or high-throughput instrumentation such as the ABI CATALYST 800 (Applied Biosystems) thermal cycler or the PTC-200 thermal cycler (MJ Research) in conjunction with the HYDRA microdispenser (Robbins Scientific) or the MICROLAB 2200 (Hamilton) liquid transfer system. cDNA sequencing reactions were prepared using reagents provided by Amersham Pharmacia Biotech or supplied in ABI sequencing kits such as the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Applied Biosystems). Electrophoretic separation of cDNA sequencing reactions and detection of labeled polynucleotides were carried out using the MEGABACE 1000 DNA sequencing system (Molecular Dynamics); the ABI PRISM 373 or 377 sequencing system (Applied Biosystems) in conjunction with standard ABI protocols and base calling software; or other sequence analysis systems known in the art. Reading frames within the cDNA sequences were identified using standard methods (reviewed in Ausubel, 1997, supra, unit 7.7). Some of the cDNA sequences were selected for extension using the techniques disclosed in Example VIII.

30 The polynucleotide sequences derived from Incyte cDNAs were validated by removing vector, linker, and poly(A) sequences and by masking ambiguous bases, using algorithms and programs based on BLAST, dynamic programming, and dinucleotide nearest neighbor analysis. The Incyte cDNA sequences or translations thereof were then queried against a selection of public databases such as the GenBank primate, rodent, mammalian, vertebrate, and eukaryote databases, 35 and BLOCKS, PRINTS, DOMO, PRODOM; PROTEOME databases with sequences from Homo

sapiens, Rattus norvegicus, Mus musculus, Caenorhabditis elegans, Saccharomyces cerevisiae, Schizosaccharomyces pombe, and Candida albicans (Incyte Genomics, Palo Alto CA); and hidden Markov model (HMM)-based protein family databases such as PFAM. (HMM is a probabilistic approach which analyzes consensus primary structures of gene families. See, for example, Eddy, 5 S.R. (1996) Curr. Opin. Struct. Biol. 6:361-365.) The queries were performed using programs based on BLAST, FASTA, BLIMPS, and HMMER. The Incyte cDNA sequences were assembled to produce full length polynucleotide sequences. Alternatively, GenBank cDNAs, GenBank ESTs, stitched sequences, stretched sequences, or Genscan-predicted coding sequences (see Examples IV and V) were used to extend Incyte cDNA assemblages to full length. Assembly was performed 10 using programs based on Phred, Phrap, and Consed, and cDNA assemblages were screened for open reading frames using programs based on GeneMark, BLAST, and FASTA. The full length polynucleotide sequences were translated to derive the corresponding full length polypeptide sequences. Alternatively, a polypeptide of the invention may begin at any of the methionine residues of the full length translated polypeptide. Full length polypeptide sequences were 15 subsequently analyzed by querying against databases such as the GenBank protein databases (genpept), SwissProt, the PROTEOME databases, BLOCKS, PRINTS, DOMO, PRODOM, Prosite, and hidden Markov model (HMM)-based protein family databases such as PFAM. Full length polynucleotide sequences are also analyzed using MACDNASIS PRO software (Hitachi Software Engineering, South San Francisco CA) and LASERGENE software (DNASTAR). Polynucleotide 20 and polypeptide sequence alignments are generated using default parameters specified by the CLUSTAL algorithm as incorporated into the MEGALIGN multisequence alignment program (DNASTAR), which also calculates the percent identity between aligned sequences.

Table 7 summarizes the tools, programs, and algorithms used for the analysis and assembly of Incyte cDNA and full length sequences and provides applicable descriptions, references, and 25 threshold parameters. The first column of Table 7 shows the tools, programs, and algorithms used, the second column provides brief descriptions thereof, the third column presents appropriate references, all of which are incorporated by reference herein in their entirety, and the fourth column presents, where applicable, the scores, probability values, and other parameters used to evaluate the strength of a match between two sequences (the higher the score or the lower the probability value, 30 the greater the identity between two sequences).

The programs described above for the assembly and analysis of full length polynucleotide and polypeptide sequences were also used to identify polynucleotide sequence fragments from SEQ ID NO:21-40. Fragments from about 20 to about 4000 nucleotides which are useful in hybridization and amplification technologies are described in Table 4, column 2.

#### 35 IV. Identification and Editing of Coding Sequences from Genomic DNA

Putative kinases and phosphatases were initially identified by running the Genscan gene identification program against public genomic sequence databases (e.g., gbpri and gbhtg). Genscan is a general-purpose gene identification program which analyzes genomic DNA sequences from a variety of organisms (See Burge, C. and S. Karlin (1997) J. Mol. Biol. 268:78-94, and Burge, C. and S. Karlin (1998) Curr. Opin. Struct. Biol. 8:346-354). The program concatenates predicted exons to form an assembled cDNA sequence extending from a methionine to a stop codon. The output of Genscan is a FASTA database of polynucleotide and polypeptide sequences. The maximum range of sequence for Genscan to analyze at once was set to 30 kb. To determine which of these Genscan predicted cDNA sequences encode kinases and phosphatases, the encoded polypeptides were analyzed by querying against PFAM models for kinases and phosphatases. Potential kinases and phosphatases were also identified by homology to Incyte cDNA sequences that had been annotated as kinases and phosphatases. These selected Genscan-predicted sequences were then compared by BLAST analysis to the genpept and gbpri public databases. Where necessary, the Genscan-predicted sequences were then edited by comparison to the top BLAST hit from genpept to correct errors in the sequence predicted by Genscan, such as extra or omitted exons. BLAST analysis was also used to find any Incyte cDNA or public cDNA coverage of the Genscan-predicted sequences, thus providing evidence for transcription. When Incyte cDNA coverage was available, this information was used to correct or confirm the Genscan predicted sequence. Full length polynucleotide sequences were obtained by assembling Genscan-predicted coding sequences with Incyte cDNA sequences and/or public cDNA sequences using the assembly process described in Example III. Alternatively, full length polynucleotide sequences were derived entirely from edited or unedited Genscan-predicted coding sequences.

#### **V. Assembly of Genomic Sequence Data with cDNA Sequence Data**

##### **"Stitched" Sequences**

Partial cDNA sequences were extended with exons predicted by the Genscan gene identification program described in Example IV. Partial cDNAs assembled as described in Example III were mapped to genomic DNA and parsed into clusters containing related cDNAs and Genscan exon predictions from one or more genomic sequences. Each cluster was analyzed using an algorithm based on graph theory and dynamic programming to integrate cDNA and genomic information, generating possible splice variants that were subsequently confirmed, edited, or extended to create a full length sequence. Sequence intervals in which the entire length of the interval was present on more than one sequence in the cluster were identified, and intervals thus identified were considered to be equivalent by transitivity. For example, if an interval was present on a cDNA and two genomic sequences, then all three intervals were considered to be equivalent. This process allows unrelated but consecutive genomic sequences to be brought together, bridged by

cDNA sequence. Intervals thus identified were then "stitched" together by the stitching algorithm in the order that they appear along their parent sequences to generate the longest possible sequence, as well as sequence variants. Linkages between intervals which proceed along one type of parent sequence (cDNA to cDNA or genomic sequence to genomic sequence) were given preference over 5 linkages which change parent type (cDNA to genomic sequence). The resultant stitched sequences were translated and compared by BLAST analysis to the genpept and gbpr public databases. Incorrect exons predicted by Genscan were corrected by comparison to the top BLAST hit from genpept. Sequences were further extended with additional cDNA sequences, or by inspection of genomic DNA, when necessary.

#### 10 **"Stretched" Sequences**

Partial DNA sequences were extended to full length with an algorithm based on BLAST analysis. First, partial cDNAs assembled as described in Example III were queried against public databases such as the GenBank primate, rodent, mammalian, vertebrate, and eukaryote databases using the BLAST program. The nearest GenBank protein homolog was then compared by BLAST 15 analysis to either Incyte cDNA sequences or GenScan exon predicted sequences described in Example IV. A chimeric protein was generated by using the resultant high-scoring segment pairs (HSPs) to map the translated sequences onto the GenBank protein homolog. Insertions or deletions may occur in the chimeric protein with respect to the original GenBank protein homolog. The GenBank protein homolog, the chimeric protein, or both were used as probes to search for 20 homologous genomic sequences from the public human genome databases. Partial DNA sequences were therefore "stretched" or extended by the addition of homologous genomic sequences. The resultant stretched sequences were examined to determine whether it contained a complete gene.

#### **VI. Chromosomal Mapping of KAP Encoding Polynucleotides**

The sequences which were used to assemble SEQ ID NO:21-40 were compared with 25 sequences from the Incyte LIFESEQ database and public domain databases using BLAST and other implementations of the Smith-Waterman algorithm. Sequences from these databases that matched SEQ ID NO:21-40 were assembled into clusters of contiguous and overlapping sequences using assembly algorithms such as Phrap (Table 7). Radiation hybrid and genetic mapping data available from public resources such as the Stanford Human Genome Center (SHGC), Whitehead Institute for 30 Genome Research (WIGR), and Généthon were used to determine if any of the clustered sequences had been previously mapped. Inclusion of a mapped sequence in a cluster resulted in the assignment of all sequences of that cluster, including its particular SEQ ID NO., to that map location.

Map locations are represented by ranges, or intervals, of human chromosomes. The map 35 position of an interval, in centiMorgans, is measured relative to the terminus of the chromosome's

p-arm. (The centiMorgan (cM) is a unit of measurement based on recombination frequencies between chromosomal markers. On average, 1 cM is roughly equivalent to 1 megabase (Mb) of DNA in humans, although this can vary widely due to hot and cold spots of recombination.) The cM distances are based on genetic markers mapped by Généthon which provide boundaries for 5 radiation hybrid markers whose sequences were included in each of the clusters. Human genome maps and other resources available to the public, such as the NCBI "GeneMap'99" World Wide Web site (<http://www.ncbi.nlm.nih.gov/genemap/>), can be employed to determine if previously identified disease genes map within or in proximity to the intervals indicated above.

In this manner, SEQ ID NO:33 was mapped to chromosome 12 within the interval from 10 97.10 to 113.30 centiMorgans. SEQ ID NO:35 was mapped to chromosome 3 within the interval from 16.50 to 30.40 centiMorgans. SEQ ID NO:29 was mapped to chromosome 13 within the interval from 11.60 to 22.80 centiMorgans, to chromosome 15 within the interval from 72.30 to 77.30 centiMorgans, and to chromosome 20 within the interval from 57.70 to 64.10 centiMorgans. More than one map location is reported for SEQ ID NO:29, indicating that sequences having 15 different map locations were assembled into a single cluster. This situation occurs, for example, when sequences having strong similarity, but not complete identity, are assembled into a single cluster.

#### VII. Analysis of Polynucleotide Expression

Northern analysis is a laboratory technique used to detect the presence of a transcript of a 20 gene and involves the hybridization of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound. (See, e.g., Sambrook, *supra*, ch. 7; Ausubel (1995) *supra*, ch. 4 and 16.)

Analogous computer techniques applying BLAST were used to search for identical or related molecules in cDNA databases such as GenBank or LIFESEQ (Incyte Genomics). This 25 analysis is much faster than multiple membrane-based hybridizations. In addition, the sensitivity of the computer search can be modified to determine whether any particular match is categorized as exact or similar. The basis of the search is the product score, which is defined as:

$$\frac{\text{BLAST Score} \times \text{Percent Identity}}{5 \times \text{minimum} \{ \text{length}(\text{Seq. 1}), \text{length}(\text{Seq. 2}) \}}$$

The product score takes into account both the degree of similarity between two sequences and the length of the sequence match. The product score is a normalized value between 0 and 100, and is calculated as follows: the BLAST score is multiplied by the percent nucleotide identity and the 35 product is divided by (5 times the length of the shorter of the two sequences). The BLAST score is



calculated by assigning a score of +5 for every base that matches in a high-scoring segment pair (HSP), and -4 for every mismatch. Two sequences may share more than one HSP (separated by gaps). If there is more than one HSP, then the pair with the highest BLAST score is used to calculate the product score. The product score represents a balance between fractional overlap and quality in a BLAST alignment. For example, a product score of 100 is produced only for 100% identity over the entire length of the shorter of the two sequences being compared. A product score of 70 is produced either by 100% identity and 70% overlap at one end, or by 88% identity and 100% overlap at the other. A product score of 50 is produced either by 100% identity and 50% overlap at one end, or 79% identity and 100% overlap.

10 Alternatively, polynucleotide sequences encoding KAP are analyzed with respect to the tissue sources from which they were derived. For example, some full length sequences are assembled, at least in part, with overlapping Incyte cDNA sequences (see Example III). Each cDNA sequence is derived from a cDNA library constructed from a human tissue. Each human tissue is classified into one of the following organ/tissue categories: cardiovascular system; connective  
15 tissue; digestive system; embryonic structures; endocrine system; exocrine glands; genitalia, female; genitalia, male; germ cells; hemic and immune system; liver; musculoskeletal system; nervous system; pancreas; respiratory system; sense organs; skin; stomatognathic system; unclassified/mixed; or urinary tract. The number of libraries in each category is counted and divided by the total number of libraries across all categories. Similarly, each human tissue is  
20 classified into one of the following disease/condition categories: cancer, cell line, developmental, inflammation, neurological, trauma, cardiovascular, pooled, and other, and the number of libraries in each category is counted and divided by the total number of libraries across all categories. The resulting percentages reflect the tissue- and disease-specific expression of cDNA encoding KAP. cDNA sequences and cDNA library/tissue information are found in the LIFESEQ GOLD database  
25 (Incyte Genomics, Palo Alto CA).

#### **VIII. Extension of KAP Encoding Polynucleotides**

Full length polynucleotide sequences were also produced by extension of an appropriate fragment of the full length molecule using oligonucleotide primers designed from this fragment. One primer was synthesized to initiate 5' extension of the known fragment, and the other primer was  
30 synthesized to initiate 3' extension of the known fragment. The initial primers were designed using OLIGO 4.06 software (National Biosciences), or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the target sequence at temperatures of about 68°C to about 72°C. Any stretch of nucleotides which would result in hairpin structures and primer-primer dimerizations was avoided.

35 Selected human cDNA libraries were used to extend the sequence. If more than one

extension was necessary or desired, additional or nested sets of primers were designed.

High fidelity amplification was obtained by PCR using methods well known in the art. PCR was performed in 96-well plates using the PTC-200 thermal cycler (MJ Research, Inc.). The reaction mix contained DNA template, 200 nmol of each primer, reaction buffer containing  $Mg^{2+}$ , 5  $(NH_4)_2SO_4$ , and 2-mercaptoethanol, Taq DNA polymerase (Amersham Pharmacia Biotech), ELONGASE enzyme (Life Technologies), and Pfu DNA polymerase (Stratagene), with the following parameters for primer pair PCI A and PCI B: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C. In the alternative, the parameters for primer pair T7 and SK+ were as follows: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 57°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C.

The concentration of DNA in each well was determined by dispensing 100  $\mu$ l PICOGREEN quantitation reagent (0.25% (v/v) PICOGREEN; Molecular Probes, Eugene OR) dissolved in 1X TE and 0.5  $\mu$ l of undiluted PCR product into each well of an opaque fluorimeter plate (Corning Costar, 15 Acton MA), allowing the DNA to bind to the reagent. The plate was scanned in a Fluoroskan II (Labsystems Oy, Helsinki, Finland) to measure the fluorescence of the sample and to quantify the concentration of DNA. A 5  $\mu$ l to 10  $\mu$ l aliquot of the reaction mixture was analyzed by electrophoresis on a 1 % agarose gel to determine which reactions were successful in extending the sequence.

20 The extended nucleotides were desalted and concentrated, transferred to 384-well plates, digested with CviII cholera virus endonuclease (Molecular Biology Research, Madison WI), and sonicated or sheared prior to religation into pUC 18 vector (Amersham Pharmacia Biotech). For shotgun sequencing, the digested nucleotides were separated on low concentration (0.6 to 0.8%) agarose gels, fragments were excised, and agar digested with Agar ACE (Promega). Extended 25 clones were religated using T4 ligase (New England Biolabs, Beverly MA) into pUC 18 vector (Amersham Pharmacia Biotech), treated with Pfu DNA polymerase (Stratagene) to fill-in restriction site overhangs, and transfected into competent *E. coli* cells. Transformed cells were selected on antibiotic-containing media, and individual colonies were picked and cultured overnight at 37°C in 384-well plates in LB/2x carb liquid media.

30 The cells were lysed, and DNA was amplified by PCR using Taq DNA polymerase (Amersham Pharmacia Biotech) and Pfu DNA polymerase (Stratagene) with the following parameters: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 72°C, 2 min; Step 5: steps 2, 3, and 4 repeated 29 times; Step 6: 72°C, 5 min; Step 7: storage at 4°C. DNA was quantified by PICOGREEN reagent (Molecular Probes) as described above. Samples with low 35 DNA recoveries were reamplified using the same conditions as described above. Samples were

diluted with 20% dimethylsulfoxide (1:2, v/v), and sequenced using DYENAMIC energy transfer sequencing primers and the DYENAMIC DIRECT kit (Amersham Pharmacia Biotech) or the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Applied Biosystems).

In like manner, full length polynucleotide sequences are verified using the above procedure or are used to obtain 5' regulatory sequences using the above procedure along with oligonucleotides designed for such extension, and an appropriate genomic library.

#### IX. Labeling and Use of Individual Hybridization Probes

Hybridization probes derived from SEQ ID NO:21-40 are employed to screen cDNAs, genomic DNAs, or mRNAs. Although the labeling of oligonucleotides, consisting of about 20 base pairs, is specifically described, essentially the same procedure is used with larger nucleotide fragments. Oligonucleotides are designed using state-of-the-art software such as OLIGO 4.06 software (National Biosciences) and labeled by combining 50 pmol of each oligomer, 250  $\mu$ Ci of [ $\gamma$ - $^{32}$ P] adenosine triphosphate (Amersham Pharmacia Biotech), and T4 polynucleotide kinase (DuPont NEN, Boston MA). The labeled oligonucleotides are substantially purified using a SEPHADEX G-25 superfine size exclusion dextran bead column (Amersham Pharmacia Biotech). An aliquot containing  $10^7$  counts per minute of the labeled probe is used in a typical membrane-based hybridization analysis of human genomic DNA digested with one of the following endonucleases: Ase I, Bgl II, Eco RI, Pst I, Xba I, or Pvu II (DuPont NEN).

The DNA from each digest is fractionated on a 0.7% agarose gel and transferred to nylon membranes (Nytran Plus, Schleicher & Schuell, Durham NH). Hybridization is carried out for 16 hours at 40°C. To remove nonspecific signals, blots are sequentially washed at room temperature under conditions of up to, for example, 0.1 x saline sodium citrate and 0.5% sodium dodecyl sulfate. Hybridization patterns are visualized using autoradiography or an alternative imaging means and compared.

#### 25 X. Microarrays

The linkage or synthesis of array elements upon a microarray can be achieved utilizing photolithography, piezoelectric printing (ink-jet printing, See, e.g., Baldeschweiler, *supra*.), mechanical microspotting technologies, and derivatives thereof. The substrate in each of the aforementioned technologies should be uniform and solid with a non-porous surface (Schena (1999), *supra*). Suggested substrates include silicon, silica, glass slides, glass chips, and silicon wafers. Alternatively, a procedure analogous to a dot or slot blot may also be used to arrange and link elements to the surface of a substrate using thermal, UV, chemical, or mechanical bonding procedures. A typical array may be produced using available methods and machines well known to those of ordinary skill in the art and may contain any appropriate number of elements. (See, e.g., Schena, M. et al. (1995) Science 270:467-470; Shalon, D. et al. (1996) Genome Res. 6:639-645;

Marshall, A. and J. Hodgson (1998) Nat. Biotechnol. 16:27-31.)

Full length cDNAs, Expressed Sequence Tags (ESTs), or fragments or oligomers thereof may comprise the elements of the microarray. Fragments or oligomers suitable for hybridization can be selected using software well known in the art such as LASERGENE software (DNASTAR).  
 5 The array elements are hybridized with polynucleotides in a biological sample. The polynucleotides in the biological sample are conjugated to a fluorescent label or other molecular tag for ease of detection. After hybridization, nonhybridized nucleotides from the biological sample are removed, and a fluorescence scanner is used to detect hybridization at each array element. Alternatively, laser desorption and mass spectrometry may be used for detection of hybridization. The degree of  
 10 complementarity and the relative abundance of each polynucleotide which hybridizes to an element on the microarray may be assessed. In one embodiment, microarray preparation and usage is described in detail below.

#### Tissue or Cell Sample Preparation

Total RNA is isolated from tissue samples using the guanidinium thiocyanate method and  
 15 poly(A)<sup>+</sup> RNA is purified using the oligo-(dT) cellulose method. Each poly(A)<sup>+</sup> RNA sample is reverse transcribed using MMLV reverse-transcriptase, 0.05 pg/ $\mu$ l oligo-(dT) primer (21mer), 1X first strand buffer, 0.03 units/ $\mu$ l RNase inhibitor, 500  $\mu$ M dATP, 500  $\mu$ M dGTP, 500  $\mu$ M dTTP, 40  $\mu$ M dCTP, 40  $\mu$ M dCTP-Cy3 (BDS) or dCTP-Cy5 (Amersham Pharmacia Biotech). The reverse transcription reaction is performed in a 25 ml volume containing 200 ng poly(A)<sup>+</sup> RNA with  
 20 GEMBRIGHT kits (Incyte). Specific control poly(A)<sup>+</sup> RNAs are synthesized by in vitro transcription from non-coding yeast genomic DNA. After incubation at 37°C for 2 hr, each reaction sample (one with Cy3 and another with Cy5 labeling) is treated with 2.5 ml of 0.5M sodium hydroxide and incubated for 20 minutes at 85°C to stop the reaction and degrade the RNA. Samples are purified using two successive CHROMA SPIN 30 gel filtration spin columns  
 25 (CLONTECH Laboratories, Inc. (CLONTECH), Palo Alto CA) and after combining, both reaction samples are ethanol precipitated using 1 ml of glycogen (1 mg/ml), 60 ml sodium acetate, and 300 ml of 100% ethanol. The sample is then dried to completion using a SpeedVAC (Savant Instruments Inc., Holbrook NY) and resuspended in 14  $\mu$ l 5X SSC/0.2% SDS.

#### Microarray Preparation

30 Sequences of the present invention are used to generate array elements. Each array element is amplified from bacterial cells containing vectors with cloned cDNA inserts. PCR amplification uses primers complementary to the vector sequences flanking the cDNA insert. Array elements are amplified in thirty cycles of PCR from an initial quantity of 1-2 ng to a final quantity greater than 5  $\mu$ g. Amplified array elements are then purified using SEPHACRYL-400 (Amersham Pharmacia  
 35 Biotech).

Purified array elements are immobilized on polymer-coated glass slides. Glass microscope slides (Corning) are cleaned by ultrasound in 0.1% SDS and acetone, with extensive distilled water washes between and after treatments. Glass slides are etched in 4% hydrofluoric acid (VWR Scientific Products Corporation (VWR), West Chester PA), washed extensively in distilled water, and coated with 0.05% aminopropyl silane (Sigma) in 95% ethanol. Coated slides are cured in a 110°C oven.

Array elements are applied to the coated glass substrate using a procedure described in U.S. Patent No. 5,807,522, incorporated herein by reference. 1  $\mu$ l of the array element DNA, at an average concentration of 100 ng/ $\mu$ l, is loaded into the open capillary printing element by a high-speed robotic apparatus. The apparatus then deposits about 5 nl of array element sample per slide.

Microarrays are UV-crosslinked using a STRATALINKER UV-crosslinker (Stratagene). Microarrays are washed at room temperature once in 0.2% SDS and three times in distilled water. Non-specific binding sites are blocked by incubation of microarrays in 0.2% casein in phosphate buffered saline (PBS) (Tropix, Inc., Bedford MA) for 30 minutes at 60°C followed by washes in 0.2% SDS and distilled water as before.

#### Hybridization

Hybridization reactions contain 9  $\mu$ l of sample mixture consisting of 0.2  $\mu$ g each of Cy3 and Cy5 labeled cDNA synthesis products in 5X SSC, 0.2% SDS hybridization buffer. The sample mixture is heated to 65°C for 5 minutes and is aliquoted onto the microarray surface and covered with an 1.8 cm<sup>2</sup> coverslip. The arrays are transferred to a waterproof chamber having a cavity just slightly larger than a microscope slide. The chamber is kept at 100% humidity internally by the addition of 140  $\mu$ l of 5X SSC in a corner of the chamber. The chamber containing the arrays is incubated for about 6.5 hours at 60°C. The arrays are washed for 10 min at 45°C in a first wash buffer (1X SSC, 0.1% SDS), three times for 10 minutes each at 45°C in a second wash buffer (0.1X SSC), and dried.

#### Detection

Reporter-labeled hybridization complexes are detected with a microscope equipped with an Innova 70 mixed gas 10 W laser (Coherent, Inc., Santa Clara CA) capable of generating spectral lines at 488 nm for excitation of Cy3 and at 632 nm for excitation of Cy5. The excitation laser light is focused on the array using a 20X microscope objective (Nikon, Inc., Melville NY). The slide containing the array is placed on a computer-controlled X-Y stage on the microscope and raster-scanned past the objective. The 1.8 cm x 1.8 cm array used in the present example is scanned with a resolution of 20 micrometers.

In two separate scans, a mixed gas multiline laser excites the two fluorophores sequentially. Emitted light is split, based on wavelength, into two photomultiplier tube detectors (PMT R1477,

Hamamatsu Photonics Systems, Bridgewater NJ) corresponding to the two fluorophores.

Appropriate filters positioned between the array and the photomultiplier tubes are used to filter the signals. The emission maxima of the fluorophores used are 565 nm for Cy3 and 650 nm for Cy5.

Each array is typically scanned twice, one scan per fluorophore using the appropriate filters at the 5 laser source, although the apparatus is capable of recording the spectra from both fluorophores simultaneously.

The sensitivity of the scans is typically calibrated using the signal intensity generated by a cDNA control species added to the sample mixture at a known concentration. A specific location on the array contains a complementary DNA sequence, allowing the intensity of the signal at that 10 location to be correlated with a weight ratio of hybridizing species of 1:100,000. When two samples from different sources (e.g., representing test and control cells), each labeled with a different fluorophore, are hybridized to a single array for the purpose of identifying genes that are differentially expressed, the calibration is done by labeling samples of the calibrating cDNA with the two fluorophores and adding identical amounts of each to the hybridization mixture.

15 The output of the photomultiplier tube is digitized using a 12-bit RTI-835H analog-to-digital (A/D) conversion board (Analog Devices, Inc., Norwood MA) installed in an IBM-compatible PC computer. The digitized data are displayed as an image where the signal intensity is mapped using a linear 20-color transformation to a pseudocolor scale ranging from blue (low signal) to red (high signal). The data is also analyzed quantitatively. Where two different 20 fluorophores are excited and measured simultaneously, the data are first corrected for optical crosstalk (due to overlapping emission spectra) between the fluorophores using each fluorophore's emission spectrum.

A grid is superimposed over the fluorescence signal image such that the signal from each spot is centered in each element of the grid. The fluorescence signal within each element is then 25 integrated to obtain a numerical value corresponding to the average intensity of the signal. The software used for signal analysis is the GEMTOOLS gene expression analysis program (Incyte).

## **XI. Complementary Polynucleotides**

Sequences complementary to the KAP-encoding sequences, or any parts thereof, are used to detect, decrease, or inhibit expression of naturally occurring KAP. Although use of 30 oligonucleotides comprising from about 15 to 30 base pairs is described, essentially the same procedure is used with smaller or with larger sequence fragments. Appropriate oligonucleotides are designed using OLIGO 4.06 software (National Biosciences) and the coding sequence of KAP. To inhibit transcription, a complementary oligonucleotide is designed from the most unique 5' sequence and used to prevent promoter binding to the coding sequence. To inhibit translation, a 35 complementary oligonucleotide is designed to prevent ribosomal binding to the KAP-encoding

transcript.

## **XII. Expression of KAP**

Expression and purification of KAP is achieved using bacterial or virus-based expression systems. For expression of KAP in bacteria, cDNA is subcloned into an appropriate vector containing an antibiotic resistance gene and an inducible promoter that directs high levels of cDNA transcription. Examples of such promoters include, but are not limited to, the *trp-lac (tac)* hybrid promoter and the T5 or T7 bacteriophage promoter in conjunction with the *lac* operator regulatory element. Recombinant vectors are transformed into suitable bacterial hosts, e.g., BL21(DE3).

Antibiotic resistant bacteria express KAP upon induction with isopropyl beta-D-thiogalactopyranoside (IPTG). Expression of KAP in eukaryotic cells is achieved by infecting insect or mammalian cell lines with recombinant Autographica californica nuclear polyhedrosis virus (AcMNPV), commonly known as baculovirus. The nonessential polyhedrin gene of baculovirus is replaced with cDNA encoding KAP by either homologous recombination or bacterial-mediated transposition involving transfer plasmid intermediates. Viral infectivity is maintained and the strong polyhedrin promoter drives high levels of cDNA transcription.

Recombinant baculovirus is used to infect Spodoptera frugiperda (Sf9) insect cells in most cases, or human hepatocytes, in some cases. Infection of the latter requires additional genetic modifications to baculovirus. (See Engelhard, E.K. et al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945.)

In most expression systems, KAP is synthesized as a fusion protein with, e.g., glutathione S-transferase (GST) or a peptide epitope tag, such as FLAG or 6-His, permitting rapid, single-step, affinity-based purification of recombinant fusion protein from crude cell lysates. GST, a 26-kilodalton enzyme from Schistosoma japonicum, enables the purification of fusion proteins on immobilized glutathione under conditions that maintain protein activity and antigenicity (Amersham Pharmacia Biotech). Following purification, the GST moiety can be proteolytically cleaved from KAP at specifically engineered sites. FLAG, an 8-amino acid peptide, enables immunoaffinity purification using commercially available monoclonal and polyclonal anti-FLAG antibodies (Eastman Kodak). 6-His, a stretch of six consecutive histidine residues, enables purification on metal-chelate resins (QIAGEN). Methods for protein expression and purification are discussed in Ausubel (1995, supra, ch. 10 and 16). Purified KAP obtained by these methods can be used directly in the assays shown in Examples XVI, XVII, XVIII, XIX, XX, and XXI where applicable.

## **XIII. Functional Assays**

KAP function is assessed by expressing the sequences encoding KAP at physiologically elevated levels in mammalian cell culture systems. cDNA is subcloned into a mammalian expression vector containing a strong promoter that drives high levels of cDNA expression. Vectors

of choice include PCMV SPORT (Life Technologies) and PCR3.1 (Invitrogen, Carlsbad CA), both of which contain the cytomegalovirus promoter. 5-10  $\mu$ g of recombinant vector are transiently transfected into a human cell line, for example, an endothelial or hematopoietic cell line, using either liposome formulations or electroporation. 1-2  $\mu$ g of an additional plasmid containing sequences encoding a marker protein are co-transfected. Expression of a marker protein provides a means to distinguish transfected cells from nontransfected cells and is a reliable predictor of cDNA expression from the recombinant vector. Marker proteins of choice include, e.g., Green Fluorescent Protein (GFP; Clontech), CD64, or a CD64-GFP fusion protein. Flow cytometry (FCM), an automated, laser optics-based technique, is used to identify transfected cells expressing GFP or CD64-GFP and to evaluate the apoptotic state of the cells and other cellular properties. FCM detects and quantifies the uptake of fluorescent molecules that diagnose events preceding or coincident with cell death. These events include changes in nuclear DNA content as measured by staining of DNA with propidium iodide; changes in cell size and granularity as measured by forward light scatter and 90 degree side light scatter; down-regulation of DNA synthesis as measured by decrease in bromodeoxyuridine uptake; alterations in expression of cell surface and intracellular proteins as measured by reactivity with specific antibodies; and alterations in plasma membrane composition as measured by the binding of fluorescein-conjugated Annexin V protein to the cell surface. Methods in flow cytometry are discussed in Ormerod, M.G. (1994) Flow Cytometry, Oxford, New York NY.

The influence of KAP on gene expression can be assessed using highly purified populations of cells transfected with sequences encoding KAP and either CD64 or CD64-GFP. CD64 and CD64-GFP are expressed on the surface of transfected cells and bind to conserved regions of human immunoglobulin G (IgG). Transfected cells are efficiently separated from nontransfected cells using magnetic beads coated with either human IgG or antibody against CD64 (DYNAL, Lake Success NY). mRNA can be purified from the cells using methods well known by those of skill in the art. Expression of mRNA encoding KAP and other genes of interest can be analyzed by northern analysis or microarray techniques.

#### **XIV. Production of KAP Specific Antibodies**

KAP substantially purified using polyacrylamide gel electrophoresis (PAGE; see, e.g., Harrington, M.G. (1990) *Methods Enzymol.* 182:488-495), or other purification techniques, is used to immunize rabbits and to produce antibodies using standard protocols.

Alternatively, the KAP amino acid sequence is analyzed using LASERGENE software (DNASTAR) to determine regions of high immunogenicity, and a corresponding oligopeptide is synthesized and used to raise antibodies by means known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions are



well described in the art. (See, e.g., Ausubel, 1995, supra, ch. 11.)

Typically, oligopeptides of about 15 residues in length are synthesized using an ABI 431A peptide synthesizer (Applied Biosystems) using Fmoc chemistry and coupled to KLH (Sigma-Aldrich, St. Louis MO) by reaction with N-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) to increase immunogenicity. (See, e.g., Ausubel, 1995, supra.) Rabbits are immunized with the oligopeptide-KLH complex in complete Freund's adjuvant. Resulting antisera are tested for antipeptide and anti-KAP activity by, for example, binding the peptide or KAP to a substrate, blocking with 1% BSA, reacting with rabbit antisera, washing, and reacting with radio-iodinated goat anti-rabbit IgG.

#### 10 XV. Purification of Naturally Occurring KAP Using Specific Antibodies

Naturally occurring or recombinant KAP is substantially purified by immunoaffinity chromatography using antibodies specific for KAP. An immunoaffinity column is constructed by covalently coupling anti-KAP antibody to an activated chromatographic resin, such as CNBr-activated SEPHAROSE (Amersham Pharmacia Biotech). After the coupling, the resin is  
15 blocked and washed according to the manufacturer's instructions.

Media containing KAP are passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of KAP (e.g., high ionic strength buffers in the presence of detergent). The column is eluted under conditions that disrupt antibody/KAP binding (e.g., a buffer of pH 2 to pH 3, or a high concentration of a chaotrope, such  
20 as urea or thiocyanate ion), and KAP is collected.

#### XVI. Identification of Molecules Which Interact with KAP

KAP, or biologically active fragments thereof, are labeled with <sup>125</sup>I Bolton-Hunter reagent. (See, e.g., Bolton, A.E. and W.M. Hunter (1973) *Biochem. J.* 133:529-539.) Candidate molecules previously arrayed in the wells of a multi-well plate are incubated with the labeled KAP, washed,  
25 and any wells with labeled KAP complex are assayed. Data obtained using different concentrations of KAP are used to calculate values for the number, affinity, and association of KAP with the candidate molecules.

Alternatively, molecules interacting with KAP are analyzed using the yeast two-hybrid system as described in Fields, S. and O. Song (1989) *Nature* 340:245-246, or using commercially  
30 available kits based on the two-hybrid system, such as the MATCHMAKER system (Clontech).

KAP may also be used in the PATHCALLING process (CuraGen Corp., New Haven CT) which employs the yeast two-hybrid system in a high-throughput manner to determine all interactions between the proteins encoded by two large libraries of genes (Nandabalan, K. et al. (2000) U.S. Patent No. 6,057,101).

#### 35 XVII. Demonstration of KAP Activity

Generally, protein kinase activity is measured by quantifying the phosphorylation of a protein substrate by KAP in the presence of  $[\gamma\text{-}^{32}\text{P}]\text{ATP}$ . KAP is incubated with the protein substrate,  $^{32}\text{P}\text{-ATP}$ , and an appropriate kinase buffer. The  $^{32}\text{P}$  incorporated into the substrate is separated from free  $^{32}\text{P}\text{-ATP}$  by electrophoresis and the incorporated  $^{32}\text{P}$  is counted using a 5 radioisotope counter. The amount of incorporated  $^{32}\text{P}$  is proportional to the activity of KAP. A determination of the specific amino acid residue phosphorylated is made by phosphoamino acid analysis of the hydrolyzed protein.

In one alternative, protein kinase activity is measured by quantifying the transfer of gamma phosphate from adenosine triphosphate (ATP) to a serine, threonine or tyrosine residue in a protein 10 substrate. The reaction occurs between a protein kinase sample with a biotinylated peptide substrate and gamma  $^{32}\text{P}\text{-ATP}$ . Following the reaction, free avidin in solution is added for binding to the biotinylated  $^{32}\text{P}\text{-peptide}$  product. The binding sample then undergoes a centrifugal ultrafiltration process with a membrane which will retain the product-avidin complex and allow passage of free gamma  $^{32}\text{P}\text{-ATP}$ . The reservoir of the centrifuged unit containing the  $^{32}\text{P}\text{-peptide}$  product as 15 retentate is then counted in a scintillation counter. This procedure allows the assay of any type of protein kinase sample, depending on the peptide substrate and kinase reaction buffer selected. This assay is provided in kit form (ASUA, Affinity Ultrafiltration Separation Assay, Transbio Corporation, Baltimore MD, U.S. Patent No. 5,869,275). Suggested substrates and their respective enzymes include but are not limited to: Histone H1 (Sigma) and  $\text{p34}^{\text{cdc}2}\text{kinase}$ , Annexin I, 20 Angiotensin (Sigma) and EGF receptor kinase, Annexin II and *src* kinase, ERK1 & ERK2 substrates and MEK, and myelin basic protein and ERK (Pearson, J.D. et al. (1991) Methods Enzymol. 200:62-81).

In another alternative, protein kinase activity of KAP is demonstrated in an assay containing KAP, 50  $\mu\text{l}$  of kinase buffer, 1  $\mu\text{g}$  substrate, such as myelin basic protein (MBP) or synthetic 25 peptide substrates, 1 mM DTT, 10  $\mu\text{g}$  ATP, and 0.5  $\mu\text{Ci}$   $[\gamma\text{-}^{32}\text{P}]\text{ATP}$ . The reaction is incubated at 30°C for 30 minutes and stopped by pipetting onto P81 paper. The unincorporated  $[\gamma\text{-}^{32}\text{P}]\text{ATP}$  is removed by washing and the incorporated radioactivity is measured using a scintillation counter. Alternatively, the reaction is stopped by heating to 100°C in the presence of SDS loading buffer and resolved on a 12% SDS polyacrylamide gel followed by autoradiography. The amount of 30 incorporated  $^{32}\text{P}$  is proportional to the activity of KAP.

In yet another alternative, adenylate kinase or guanylate kinase activity of KAP may be measured by the incorporation of  $^{32}\text{P}$  from  $[\gamma\text{-}^{32}\text{P}]\text{ATP}$  into ADP or GDP using a gamma radioisotope counter. KAP, in a kinase buffer, is incubated together with the appropriate nucleotide mono-phosphate substrate (AMP or GMP) and  $^{32}\text{P}$ -labeled ATP as the phosphate donor. The 35 reaction is incubated at 37°C and terminated by addition of trichloroacetic acid. The acid extract is

neutralized and subjected to gel electrophoresis to separate the mono-, di-, and triphosphonucleotide fractions. The diphosphonucleotide fraction is excised and counted. The radioactivity recovered is proportional to the activity of KAP.

In yet another alternative, other assays for KAP include scintillation proximity assays (SPA), scintillation plate technology and filter binding assays. Useful substrates include recombinant proteins tagged with glutathione transferase, or synthetic peptide substrates tagged with biotin. Inhibitors of KAP activity, such as small organic molecules, proteins or peptides, may be identified by such assays.

In another alternative, phosphatase activity of KAP is measured by the hydrolysis of para-nitrophenyl phosphate (PNPP). KAP is incubated together with PNPP in HEPES buffer pH 7.5, in the presence of 0.1%  $\beta$ -mercaptoethanol at 37°C for 60 min. The reaction is stopped by the addition of 6 ml of 10 N NaOH (Diamond, R.H. et al. (1994) *Mol. Cell. Biol.* 14:3752-62). Alternatively, acid phosphatase activity of KAP is demonstrated by incubating KAP-containing extract with 100  $\mu$ l of 10 mM PNPP in 0.1 M sodium citrate, pH 4.5, and 50  $\mu$ l of 40 mM NaCl at 37°C for 20 min. The reaction is stopped by the addition of 0.5 ml of 0.4 M glycine/NaOH, pH 10.4 (Saftig, P. et al. (1997) *J. Biol. Chem.* 272:18628-18635). The increase in light absorbance at 410 nm resulting from the hydrolysis of PNPP is measured using a spectrophotometer. The increase in light absorbance is proportional to the activity of KAP in the assay.

In the alternative, KAP activity is determined by measuring the amount of phosphate removed from a phosphorylated protein substrate. Reactions are performed with 2 or 4 nM KAP in a final volume of 30  $\mu$ l containing 60 mM Tris, pH 7.6, 1 mM EDTA, 1 mM EGTA, 0.1%  $\beta$ -mercaptoethanol and 10  $\mu$ M substrate,  $^{32}$ P-labeled on serine/threonine or tyrosine, as appropriate. Reactions are initiated with substrate and incubated at 30° C for 10-15 min. Reactions are quenched with 450  $\mu$ l of 4% (w/v) activated charcoal in 0.6 M HCl, 90 mM  $\text{Na}_4\text{P}_2\text{O}_7$ , and 2 mM  $\text{NaH}_2\text{PO}_4$ , then centrifuged at 12,000  $\times g$  for 5 min. Acid-soluble  $^{32}\text{Pi}$  is quantified by liquid scintillation counting (Sinclair, C. et al. (1999) *J. Biol. Chem.* 274:23666-23672).

#### XVIII. Kinase Binding Assay

Binding of KAP to a FLAG-CD44 cyt fusion protein can be determined by incubating KAP with anti-KAP-conjugated immunoaffinity beads followed by incubating portions of the beads (having 10-20 ng of protein) with 0.5 ml of a binding buffer (20 mM Tris-HCL (pH 7.4), 150 mM NaCl, 0.1% bovine serum albumin, and 0.05% Triton X-100) in the presence of  $^{125}\text{I}$ -labeled FLAG-CD44cyt fusion protein (5,000 cpm/ng protein ) at 4 °C for 5 hours. Following binding, beads were washed thoroughly in the binding buffer and the bead-bound radioactivity measured in a scintillation counter (Bourguignon, L.Y.W. et al. (2001) *J. Biol. Chem.* 276:7327-7336). The amount of incorporated  $^{32}\text{P}$  is proportional to the amount of bound KAP.

**XIX. Identification of KAP Inhibitors**

Compounds to be tested are arrayed in the wells of a 384-well plate in varying concentrations along with an appropriate buffer and substrate, as described in the assays in Example XVII. KAP activity is measured for each well and the ability of each compound to inhibit KAP activity can be determined, as well as the dose-response kinetics. This assay could also be used to identify molecules which enhance KAP activity.

**XX. Identification of KAP Substrates**

A KAP "substrate-trapping" assay takes advantage of the increased substrate affinity that may be conferred by certain mutations in the PTP signature sequence of protein tyrosine phosphatases. KAP bearing these mutations form a stable complex with their substrate; this complex may be isolated biochemically. Site-directed mutagenesis of invariant residues in the PTP signature sequence in a clone encoding the catalytic domain of KAP is performed using a method standard in the art or a commercial kit, such as the MUTA-GENE kit from BIO-RAD. For expression of KAP mutants in *Escherichia coli*, DNA fragments containing the mutation are exchanged with the corresponding wild-type sequence in an expression vector bearing the sequence encoding KAP or a glutathione S-transferase (GST)-KAP fusion protein. KAP mutants are expressed in *E. coli* and purified by chromatography.

The expression vector is transfected into COS1 or 293 cells via calcium phosphate-mediated transfection with 20  $\mu$ g of CsCl-purified DNA per 10-cm dish of cells or 8  $\mu$ g per 6-cm dish. Forty-eight hours after transfection, cells are stimulated with 100 ng/ml epidermal growth factor to increase tyrosine phosphorylation in cells, as the tyrosine kinase EGFR is abundant in COS cells. Cells are lysed in 50 mM Tris-HCl, pH 7.5/5 mM EDTA/150 mM NaCl/1% Triton X-100/5 mM iodoacetic acid/10 mM sodium phosphate/10 mM NaF/5  $\mu$ g/ml leupeptin/5  $\mu$ g/ml aprotinin/1 mM benzamidine (1 ml per 10-cm dish, 0.5 ml per 6-cm dish). KAP is immunoprecipitated from lysates with an appropriate antibody. GST-KAP fusion proteins are precipitated with glutathione-Sepharose, 4  $\mu$ g of mAb or 10  $\mu$ l of beads respectively per mg of cell lysate. Complexes can be visualized by PAGE or further purified to identify substrate molecules (Flint, A.J. et al. (1997) Proc. Natl. Acad. Sci. USA 94:1680-1685).

**XXI. Enhancement/Inhibition of Protein Kinase Activity**

Agonists or antagonists of KAP activation or inhibition may be tested using assays described in section XVII. Agonists cause an increase in KAP activity and antagonists cause a decrease in KAP activity.

Various modifications and variations of the described methods and systems of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the

invention. Although the invention has been described in connection with certain embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in molecular biology or related fields are intended to be within  
5 the scope of the following claims.

Table 1

Incyte Project ID	Polypeptide SEQ ID NO:	Incyte Polypeptide ID	Polynucleotide SEQ ID NO:	Incyte Polynucleotide ID
4615110	1	4615110CD1	21	4615110CB1
4622229	2	4622229CD1	22	4622229CB1
72358203	3	72358203CD1	23	72358203CB1
4885040	4	4885040CD1	24	4885040CB1
7484507	5	7484507CD1	25	7484507CB1
7198931	6	7198931CD1	26	7198931CB1
7482905	7	7482905CD1	27	7482905CB1
7483019	8	7483019CD1	28	7483019CB1
5455490	9	5455490CD1	29	5455490CB1
5547067	10	5547067CD1	30	5547067CB1
71675660	11	71675660CD1	31	71675660CB1
71678683	12	71678683CD1	32	71678683CB1
7474567	13	7474567CD1	33	7474567CB1
3838946	14	3838946CD1	34	3838946CB1
72001176	15	72001176CD1	35	72001176CB1
55064363	16	55064363CD1	36	55064363CB1
7482044	17	7482044CD1	37	7482044CB1
7476595	18	7476595CD1	38	7476595CB1
71824382	19	71824382CD1	39	71824382CB1
3566882	20	3566882CD1	40	3566882CB1

Table 2

Polypeptide SEQ ID NO:	Incyte Polypeptide ID	GenBank ID NO: or PROTEOME ID NO:	Probability Score	Annotation
1	4615110CD1	g3598974	0	[Rattus norvegicus] protein tyrosine phosphatase TD14. Cao, L. et al. (1998) J. Biol. Chem. 273:21077-21083
2	4622229CD1	g4079673	0	myotubularin related 1 [Homo sapiens]. Kioschis, P. et al. (1998) Genomics 54:256-266
3	72358203CD1	g7768151	6.40E-17	Protein phosphatase 2C (PP2C) [Fagus sylvatica].
4	4885040CD1	g6468206	1.20E-119	[Mus musculus] thiamin pyrophosphokinase. Nosaka, K. et al. (1999) J. Biol. Chem. 274:34129-34133
5	7484507CD1	g7649810	7.20E-14	[Homo sapiens] protein kinase PAK5
6	7198931CD1	g2815888	0	[Homo sapiens] MEK kinase 1. Xia, Y. et al. (1998) Genes Dev. 12:3369-3381
7	7482905CD1	g256855	2.10E-161	[Mus sp.] serine/threonine- and tyrosine-specific protein kinase, Nek1=NIMA cell cycle regulator homolog. Letwin, K., et al. (1992) EMBO J. 11:3521-3531
8	7483019CD1	g6552404	8.40E-197	[Rattus norvegicus] DLG6 alpha. Inagaki, H. et al. (1999) Biochem. Biophys. Res. Commun. 265:462-468
9	5455490CD1	g406058	0	protein kinase [Mus musculus]. (Walden, P.D. and Cowan, N.J. (1993) Mol. Cell. Biol. 13: 7625-7635)
10	5547067CD1	g1033033	5.90E-41	ribosomal S6 kinase [Homo sapiens]. (Zhao, Y. et al. (1995) Mol. Cell. Biol. 15: 4353-4363)
11	71675660CD1	g2738898	9.40E-175	protein kinase [Mus musculus]. (Kueng, P. et al. (1997) J. Cell Biol. 139: 1851-1859)
12	71678683CD1	g2738898	4.00E-174	protein kinase [Mus musculus]. (Kueng, P. et al. (1997) J. Cell Biol. 139: 1851-1859)
13	7474567CD1	g6723964	2.50E-72	putative serine/threonine protein kinase [Schizosaccharomyces pombe]
14	3838946CD1	g4982155	2.80E-53	glycerate kinase, putative [Thermotoga maritima]. (Nelson, K.E. et al. (1999) Nature 399: 323-329)
15	72001176CD1	g11177010	5.70E-232	casein kinase I gamma 1L [Homo sapiens]

Table 2

Polypeptide SEQ ID NO:	Incyte Polypeptide ID	GenBank ID NO: or PROTEOME ID NO:	Probability Score	Annotation
16	55064363CD1	g1679668	0	Mitogen-activated kinase kinase kinase 5 [Homo sapiens] (Wang, X.S. et al. (1996) J. Biol. Chem. 271:31607-31611)
17	7482044CD1	g11527775	0	Mitogen-activated protein kinase kinase kinase [Homo sapiens]
18	7476595CD1	g406058	0	[Mus musculus] protein kinase. Walden, P.D. and Cowan, N.J. (1993) A Novel 205-kDa Testis-specific Serine/Threonine Protein Kinase Associated with Microtubules of the Spermatid Manchette. Mol. Cell. Biol. 13, 7625-7635



Table 3

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
1	4615110CD1	1636	S86 S101 S136 S193 S275 S311 S429 S455 S487 S546 S645 S869 S1056 S1122 S1218 S1231 S1238 S1247 S1290 S1322 S1342 S1475 S1506 S1533 S1575 S1593 S1625 T95 T293 T352 T434 T450 T486 T511 T882 T1068 T1144 T1269 T1305 T1328 T1354 Y272 Y320 Y1165 Y1229	N652 N1245 N1634	Protein-tyrosine phosphatase: Y1217-R1451	HMIMER_PFAM
					Tyrosine specific protein phosphatases proteins BL00383: K1220-V1234, D1241-V1249, D1272-V1282, H1349-P1361, V1390-G1400, R1429-F1444	BLIMPS_BLOCKS
					Tyrosine specific protein phosphatases signature and profiles: L1367-M1428	PROFILERSCAN
					Protein tyrosine phosphatase signature PR00700: D1242-V1249, I1259-E1279, R1345-D1362, P1387-L1405, P1419-H1434, M1435-C1445	BLIMPS_PRINTS
					PROTEIN TYROSINE PHOSPHATASE TD14 EC 3.1.3.48 HYDROLASE PD180360: F967-L1219	BLAST_PRODROM

Table 3

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
1	cont				PROTEIN TYROSINE PHOSPHATASE TD14 EC 3.1.3.48 HYDROLASE PD184907: K713-G952	BLAST_PRODOM
					PROTEIN TYROSINE PHOSPHATASE TD14 EC 3.1.3.48 HYDROLASE PD169419: A1567-T1636	BLAST_PRODOM
					PROTEIN-TYROSINE-PHOSPHATASE DM00089 P17706 4-277: K1220-V1450	BLAST_DOMO
					PROTEIN-TYROSINE-PHOSPHATASE DM00089 P26045 632-904: K1220-Q1455	BLAST_DOMO
					PROTEIN-TYROSINE-PHOSPHATASE DM00089 P29074 641-914: K1220-Q1455	BLAST_DOMO
					PROTEIN-TYROSINE-PHOSPHATASE DM00089 P43378 285-577: K1220-Q1455	BLAST_DOMO
					Tyrosine specific protein phosphatases active site: V1390-F1402	MOTIFS
2	4622229CD1	673	S53 S113 S163 S172 S225 S253 S261 S278 S342 S354 S391 S402 S410 S437 S525 S575 S600 S654 S656 T136 T334 T358 T470 T476 T536 Y331 Y400 Y563	N78 N251 N359	Transmembrane domains: W517-S543; N-terminus is cytosolic	TMAP

Table 3

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
2					Tyrosine specific protein phosphatases proteins BL00383: W570-D578, Q511-R521, V444-A454	BLIMPS_BLOCKS
					Tyrosine specific protein phosphatases signature and profiles: L424-K480	PROFILES SCAN
					HYDROLASE PROTEIN MYOTUBULARIN DISEASE MUTATION F53A2.8 PROTEIN TYROSINE PHOSPHATASE C19A8.03 CPA2NNF1 PD014611: C178-Y372, D504-H591	BLAST_PRODROM
					MYOTUBULARIN DISEASE MUTATION HYDROLASE PD14999: H601-T671	BLAST_PRODROM
					Tyrosine specific protein phosphatases active site: V444-L456	MOTIFS
3	72358203CD1	459	S50, T257, T278, S306, T364, S430, S438		Protein phosphatase 2C: Q326-K415, L187-L265	HMMER-PFAM
					Protein phosphatase 2C: BL01032: Y120-G129, L187-G204, G214-S223, N232-E271, R328-D341, D376-D388	BLIMPS-BLOCKS
					PROTEIN PHOSPHATASE 2C MAGNESIUM HYDROLASE MANGANESE MULTIGENE FAMILY PP2C ISOFORM: PD001101: G322-L403, Y120-D289	BLAST-PRODROM

Table 3

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
3					PROTEIN PHOSPHATASE 2C: DM00377 P49596 1-295: A191-I262, R328-S456, Y120-E149	BLAST-DOMO
4	4885040CD1	243	S74 S92 T6 T56 T176	N203	Ribokinase signature PR00990 V121-F132	BLIMPS_PRINTS
					THIAMIN PYROPHOSPHOKINASE PUTATIVE TPK KINASE, PD106295: H170-M239 ; PD036502: L21-Q144	BLAST_PRODOME
5	7484507CD1	632	S6 S20 S114 S212 S231 S244 S251 S283 S300 S318 S504 S575 S587 S601 S607 T12 T183 T258 T269 T287 T338 T418	N208	Eukaryotic protein kinase domain: V55-L173, W201-L297	HMMER_PFAM
					Transmembrane domains: E421-N448 M472-G487, N terminus cytosolic	TMAP
					Tyrosine kinase catalytic domain PROO109 , Y147-L165, F197-L207, S215-E237	BLIMPS_PRINTS
					PHOSPHORYLASE KINASE ALP PD01841: L422-L458, A464-I505, G567-L603, E23-E72, L142-E193	BLIMPS_PRODOME

Table 3

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
5					PROTEIN KINASE DOMAIN DM00004; P51955 10-261: V30-M233; S43968 28-311: Q33-K289, R271-I288 A55480 28-320: Q33-K289, R271-L297; P49186 28-320: Q33-K289, R271-L297	BLAST_DOMO
6	719893ICD1	1511	S35 S118 S232 S258 S275 S281 S300 S394 S397 S398 S429 S434 S507 S514 S531 S588 S669 S782 S816 S823 S900 S923 S928 S1025 S1038 S1087 S1088 S1129 S1130 S1281 T20 T169 T261 T304 T379 T457 T657 T705 T911 T946 T996 T1020 T1069 T1113 T1147 T1165 T1279 Y1166	N346 N540 N744 N806 N1068 N1085 N1099 N1128 N1278 N1347	Eukaryotic protein kinase domain: W1242-F1507	HMMER_PFAM
					Transmembrane domains: S348-L368, A1392-L1420; N-terminus is cytosolic	TMAP
					Protein kinases signatures and profile: V1344-G1398	PROFILES SCAN

Table 3

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
6 cont					Tyrosine kinase catalytic domain signature PR00109: L1476-S1498, Y1358-I1376, G1410-L1420, C1429-E1451	BLIMPS_PRINTS
					MAPK/ERK KINASE 1 EC 2.7.1. MEK MEKK TRANSFERASE SERINE/THREONINE PROTEIN ATP BINDING PHOSPHORYLATION PD144583: M1-E601	BLAST_PRODOM
					MAPK/ERK KINASE 1 EC 2.7.1. MEK MEKK TRANSFERASE SERINE/THREONINE PROTEIN ATP BINDING PHOSPHORYLATION PD146039: Q624-Q1247	BLAST_PRODOM
					PROTEIN KINASE DOMAIN DM00004 P53349 405-658: K1244-S1498	BLAST_DOMO
					PROTEIN KINASE DOMAIN DM00004 A48084 98-348: K1244-R1495	BLAST_DOMO
					PROTEIN KINASE DOMAIN DM00004 Q01389 1176-1430: L1243-P1496	BLAST_DOMO
					PROTEIN KINASE DOMAIN DM00004 Q10407 826-1084: L1243-L1488	BLAST_DOMO
					Protein kinases ATP-binding region signature: I1248 K1271	MOTIFS
					Serine/Threonine protein kinases active-site signature: I1364-I1376	MOTIFS

Table 3

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
7	7482905CD1	830	S54 S179 S260 S279 S280 S327 S352 S370 S378 S440 S457 S525 S545 S580 S624 S664 S698 S708 S741 S747 T267 T354 T358 T403 T481 T490 T512 T634 T640 T674	N159 N303 N401 N540 N715	signal_cleavage: M1-S54	SPSCAN
					SERINE/THREONINE PROTEIN KINASE NEK1 EC 2.7.1. NIMA RELATED PROTEIN 1 TRANSFERASE ATP BINDING MITOSIS NUCLEAR PHOSPHORYLATION CELL CYCLE DIVISION TYROSINE PROTEIN PD144030: M1-L394	BLAST_PRODOM
8	7483019CD1	455	S142 S200 S208 S242 S308 S374 S421 S450 T16 T280 T283 Y307 Y317 Y359	N419	Guanylate kinase: T281-Y385	HMMER_PFAM
					PDZ domain: I3-V83	HMMER_PFAM
					Guanylate kinase protein BL00856:	BLIMPS_BLOCKS
					SH3 domain signature PR00452: A115-Q130, D132-I141, C147-R159	BLIMPS_PRINTS

Table 3

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
8					PROTEIN DOMAIN SH3 KINASE GUANYLATE TRANSFERASE ATP BINDING REPEAT GMP MEMBRANE PD001338: T280-Q373	BLAST_PRODUM
cont					PROTEIN MAGUK P55 SUBFAMILY MEMBER MPP3 DISCS LARGE HOMOLOG SH3 PD090357: P169-T280	BLAST_PRODUM
					PROTEIN MAGUK P55 SUBFAMILY MEMBER DISCS LARGE HOMOLOG SH3 DOMAIN PD152180: V94-Q161	BLAST_PRODUM
					GUANYLATE KINASE DM00755 A57653 370-570: P241-P444	BLAST_DOMO
					GUANYLATE KINASE DM00755 P54936 769-955: R246-K372, M388-P444	BLAST_DOMO
					GUANYLATE KINASE DM00755 38757 709-898: R246-P444	BLAST_DOMO
					GUANYLATE KINASE DM00755 P31007 765-954: R246-P444	BLAST_DOMO
					Guanylate kinase signature: T280-V297	MOTIFS



Table 3

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
9	5455490CD1	1720	S75 S82 S86 S115 S119 S140 S152 S175 S203 S402 S425 S430 S455 S697 S728 S733 S739 S747 S768 S776 S782 S796 S831 S836 S853 S1006 S1022 S1117 S1127 S1136 S1147 S1151 S1152 S1178 S1194 S1254 S1259 S1340 S1347 S1351 S1369 S1381 S1413 S1425 S1426 S1463 S1572 S1579 S1582 S1593 S1620 S1639 S1693 T188 T428 T436 T487 T503 T651 T681 T708 T737 T793 T838 T847 T871 T936 T958 T962 T1039 T1111 T1158 T1166 T1346 T1402 T1597 T1687	N1115 N1174 N1215	Signal Peptide: M1-S68	SPSCAN
					Signal Peptide: M31-S56	HMMER

Table 3

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
9					PDZ domain (or DHR, or GLGF): P1026-L1113	HMMER_PFAM
cont					Eukaryotic protein kinase domain: F434-F707	HMMER_PFAM
					Transmembrane domains: V328-E350, D629-F647; N terminus is cytosolic.	TMAP
					Protein kinases signatures and profile: F501-I581	PROFILES SCAN
					Tyrosine kinase catalytic domain sig: PR00109: M511-K524, Y547-I565, V628-D650	BLIMPS_PRINTS
					MICROTUBULE ASSOCIATED TESTIS SPECIFIC SERINE/THREONINE KINASE PD142315: H1235-T1720; PD182663: E785-H1061; PD135564: C83-Y242; PD041650: K243-D433	BLAST_PROD OM
					PROTEIN KINASE DOMAIN : DM00004 A54602 455-712: T436-G694; DM08046 P05986 1-397: S430-K580; DM00004 S42867 75-498: I437-T588; DM00004 S42864 41-325: E435-K580, H594-T695	BLAST_DOMO
					Serine/Threonine protein kinases active-site signature: I553-I565	MOTIFS

Table 3

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
10	5547067CD1	449	S17 S45 S89 S107 S208 S244 S358 S425 T86 T167 T187 T337 T356		Eukaryotic protein kinase domain: L146-F398	HMMER_PFAM
					Transmembrane domains: S244-R267, D324-P341; N terminus is cytosolic.	TMAP
					Protein kinases signatures and profile: F248-A297	PROFLESCAN
					Tyrosine kinase catalytic domain signature , PR00109: Y258-L276, G304-L314, A323-E345	BLIMPS_PRINTS
					PROTEIN KINASE DOMAIN: DM00004 A53300 64-305: L146-L386; DM08046 P06244 1-396: Q144-F435; DM00004 A57459 61-302: L146-L386; DM00004 S56639 153-391: I148-L386	BLAST_DOMO
					Serine/Threonine protein kinases active-site signature: I264-L276	MOTIFS
					Eukaryotic protein kinase domain: Y12-L272	HMMER_PFAM
11	71675660CD1	358	S31 S158 S258 S284 S349 T48 T340 Y293	N240	Transmembrane domain: V196-M224; N terminus is non-cytosolic.	TMAP
					Protein kinases signatures and profile: D111-S165	PROFLESCAN

Table 3

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
11					Tyrosine kinase catalytic domain signature : PR00109: M90-K103, Y126-L144, L241-I263	BLIMPS_PRINTS
cont					TESTIS SPECIFIC SERINE/ THREONINE KINASE 2 PROTEIN KINASE; PD029090: L272-T358	BLAST_PRODROM
					PROTEIN KINASE DOMAIN : DM00004 p27448 58-297: L18-L253; DM00004 JC1446 20-261: V14-I263; DM00004 S24578 18-262: V14-I263; DM00004 I48609 55-294: L18-R260	BLAST_DOMO
					Serine/Threonine protein kinases active-site signature: I132-L144	MOTIFS
					Protein kinases ATP-binding region signature: L18-K41	MOTIFS
					Eukaryotic protein kinase domain: Y12-L272	HMMER_PFAM
12	71678683CD1	358	S31 S158 S258 S284 S349 T48 T340 Y293	N240	Transmembrane domain: V196-M224; N terminus is non-cytosolic.	TMAP
					Protein kinases signatures and profile: D111-S165	PROFILESKAN
					Tyrosine kinase catalytic domain signature , PR00109: M90-K103, Y126-L144, G177-L187, Y197-S219, L241-I263	BLIMPS_PRINTS

Table 3

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
12 cont					TESTIS SPECIFIC SERINE/ THREONINE KINASE 2 PROTEIN KINASE, PD029090: L272-T358	BLAST_PRODOM
					PROTEIN KINASE DOMAIN : DM00004 p27448 58-297: L18-L253; DM00004 JC1446 20-261: V14-I263; DM00004 S24578 18-262: V14-I263; DM00004 48609 55-294: L18-R260	BLAST_DOMO
					Serine/Threonine protein kinases active-site signature: I132-L144	MOTIFS
					Protein kinases ATP-binding region signature: L18-K41	MOTIFS
13	7474567CD1	929	S56 S85 S171 S207 S483 S660 S677 T53 T57 T245 T313 T401 T440 T555 T608 T658 T679 T712 T722 T737 T760 T765	N51 N187 N630 N726 N768 N916	Eukaryotic protein kinase domain: L159-F327, F327-H106	HMMER_PPFAM
					Tyrosine kinase catalytic domain signature, PR00109: L168-L186, S247-V269, I296-A318	BLIMPS_PRINTS
14	3838946CD1	523	S283 S289 S367 S417 T166 T191 T208 T214 Y328	N487	Transmembrane domain: E163-L183, N-terminus is non-cytosolic	TMAP

Table 3

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
14 cont					HYDROXYPYRUVATE REDUCTASE PLASMD OXIDOREDUCTASE NADP PROTEIN GLYCERATE KINASE, PD014236: K131-T357, T357-L520	BLAST_PRODUM
15	72001176CD1	459	S96 S124 S150 S229 S373 T14 T137 T199 T214 T258 T269 T273 T355 T411 T454	N370 N388	Eukaryotic protein kinase domain: F44-E276	HMMER_PFAM
					Transmembrane domain: D133-I161 N-terminus is cytosolic.	TMAP
					Protein kinases signatures and profile: T140-E198	PROFILES SCAN
					CASEIN KINASE I, GAMMA 1 ISOFORM EC 2.7.1. GAMMA TRANSFERASE SERINE/THREONINE ATP BINDING MULTIGENE FAMILY PHOSPHORYLATION; PD049080: M1-N43, PD015080: F315-W379	BLAST_PRODUM
					PROTEIN KINASE DOMAIN: DM00004 A5671 46-303: V46-Y304; DM00004 C5671 45-301: V46-Y304; DM00004 B5671 48-303: V46-Y304; DM00004 D56406 31-276: V46-V293	BLAST_DOMO
					Protein kinases ATP-binding region signature: L50-K73	MOTIFS
					Serine/Threonine protein kinases active-site signature: L160-I172	MOTIFS

Table 3

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
16	55064363CD1	1360	S23 S56 S212 S253 S338 S382 S432 S486 S550 S609 S625 S632 S655 S677 S762 S843 S934 S991 S1025 S1031 S1040 S1041 S1056 S1084 T48 T205 T218 T428 T466 T545 T685 T796 T842 T887 T893 T945 T983 T1234 T1287 T1314 T1323 Y810 Y1313	N381 N620	Eukaryotic protein kinase domain: V704-L955	HMMER-PFAM
					Transmembrane domains: S445-T466, S1129-V1146; N-terminus is cytosolic	TMAP
					Protein kinases signature: T796-G848	ProfileScan
					Protein kinases ATP-binding region signature: L705-K728	MOTIFS
					Serine/Threonine protein kinases active-site signature: I816-V828	MOTIFS
					Tyrosine kinase catalytic domain signature PR00109: M773-R786, Y810-V828, G858-I868, A879-L901, L924-T946	BLIMPS-PRINTS
					Kinase, apoptosis, ASK1, MEK signal-regulating, mitogen-activated, MEKK5, MAP/ERK, MAPKKK5 PD018410: V75-N620	BLAST-PRODOM

Table 3

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
16 cont					Kinase, apoptosis, ASK1, MEK signal-regulating, mitogen-activated, MEKK5, MAP/ERK, MAPKKK5 PD014104:P982-G1205	BLAST-PRODOM
					Kinase, apoptosis, ASK1, MEK signal-regulating, mitogen-activated, MEKK5, MAP/ERK, MAPKKK5 PD024456:E1215-R1348	BLAST-PRODOM
					Kinase, apoptosis, ASK1, MEK signal-regulating, mitogen-activated, MEKK5, MAP/ERK, MAPKKK5 PD012471:F621-D697	BLAST-PRODOM
					Protein kinase domains: DM00004 A48084 98-348: V704-R943; DM00004 Q01389 1176-1430: V704-T945; DM00004 Q10407 826-1084: V704-T945; DM00004 P41892 11-249: L705-T946	BLAST-DOMO
17	7482044CD1	1345	S31 S35 S191 S250 S323 S338 S517 S600 S625 S1131 S1160 S1165 T67 T136 T154 T174 T203 T218 T268 T333 T396 T459 T492 T1161 T1201 T1231 T1251 T1273 T1294 Y428		Eukaryotic protein kinase domain:L181-F439	HMMER-PFAM



Table 3

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
17					Transmembrane domain: A868-A890; N-terminus is cytosolic	TMAP
cont					Protein kinases signature: L284-F339	ProfileScan
					Serine/Threonine protein kinases active-site signature: I305-I317	MOTIFS
					Leucine zipper pattern: L826-L847	MOTIFS
					Protein kinase domains: DM00004 A48084 98-348; V704-R943; DM00004 Q01389 1176-1430; V704-T945; DM00004 Q10407 826-1084; V704-T945; DM00004 P41892 11-249; L705-T946; DM00004 P51957 8-251; L187-R427, DM00004 P41892 11-249; L187-V395, DM00004 Q05609 553-797; E186-C419	BLAST-DOMO

Table 3

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
18	7476595CD1	2038	S18 S28 S324 S329 S335 S365 S407 S448 S536 S562 S647 S657 S666 S669 S674 S680 S707 S721 S728 S731 S780 S785 S871 S878 S882 S895 S903 S930 S938 S974 S1000 S1007 S1027 S1073 S1109 S1182 S1199 S1231 S1262 S1270 S1278 S1305 S1340 S1389 S1398 S1514 S1517 S1574 S1583 S1590 S1606 S1629 S1650 S1660 S1745 S1863 S1879 S1899 S1913 S1938 S1960 S2028 T32 T83 T99 T247 T333 T343 T349 T435 T465 T511 T569 T641 T695 T886 T1059 T1079 T1177 T1184 T1321 T1327 T1395 T1407 T1420 T1436 T1554 T1692 T1753 T1769 T1780 T1790 T1844 T1931 T1971 T2006 Y1794	N16 N645 N703 N740 N1266 N1282 N1473	PDZ domain (Also known as DHR or GLGF): Q555-F643	HMMER_PFAM

Table 3

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
18					Eukaryotic protein kinase domain: F30-F303	HMME PFAM
cont					TMAP: D225-F243; N-terminus is cytosolic	TMAP
					Protein kinases signatures and profile protein: F97-V177	PROFILES CAN
					Tyrosine kinase catalytic domain signature PR00109: M107-K120, Y143-V161, V224-D246, P269-T291	BLIMPS PRINTS
					MICROTUBULE ASSOCIATED TESTIS SPECIFIC SERINE/THREONINE PROTEIN KINASE 205KD TESTISSPECIFIC SERINE/THREONINE PROTEIN KINASE MAST205 KINASE, PD142315: H760-A1021, P1578-P1716, P1498-P1609, PD069998: T639- D734, PD182663: E499-N591	BLAST_PROD OM
					PROTEIN KINASE SERINE/THREONINE KIN4 MICROTUBULE ASSOCIATED TESTIS SPECIFIC TESTISSPECIFIC MAST205, PD040805: L306-N374	BLAST_PROD OM
					PROTEIN KINASE DOMAIN; DM00004 A54602 455-712: T32-G290; DM00004 S42867 75-498: I33-K176, H190-F331; DM08046 P05986 1-397: S28-K176, V203-D351; DM08046 P06244 1-396: D29-K176, V203-F354	BLAST_DOMO
					ATP/GTP-binding site motif A (P-loop): A1450-T1457	MOTIFS

Table 3

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
18 cont					Serine/Threonine protein kinases active-site signature: I149-V161	MOTIFS
19	71824382CD1	1770	S167 S286 S344 S364 S369 S411 S459 S475 S507 S555 S616 S705 S750 S752 S781 S813 S877 S884 S917 S926 S940 S977 S997 S1013 S1193 S1322 S1334 S1357 S1457 S1568 S1583 S1658 S1673 S1694 S1702 S1731 S1751 T30 T64 T423 T591 T624 T691 T746 T780 T788 T959 T1011 T1032 T1050 T1121 T1223 T1293 T1543 T1763 Y358 Y1252	N560 N792 N854 N1680 N1739 N1742	CNH domain: K1266-K1550	HMIMER_PFAM
					Phorbol esters/diacylglycerol binding domain: H1051-C1100	HMIMER_PFAM
					PH domain: T1121-K1239	HMIMER_PFAM
					Eukaryotic protein kinase domain: F77-F343	HMIMER_PFAM
					Protein kinase C terminal domain: S344-D372	HMIMER_PFAM

Table 3

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
19 cont					Phorbol esters / diacylglycerol binding domain dag_pe_binding_domain: C1064-A1122	PROFILES SCAN
					Tyrosine kinase catalytic domain signature PR00109: M154-S167, S191-M209, C263-E285	BLIMPS_PRINTS
					Domain found in NIK1-lik PF00780B: I738-I780 PF00780F: T1050-A1096 PF00780G: K1195-H1238 PF00780I: M1485-N1514	BLIMPS_PFAM
					MYOTONIC DYSTROPHY KINASE-RELATED CDC42-BINDING KINASE PHORBOLESTER BINDING KIAA0451 PROTEIN PD143271: R1643-P1770	BLAST_PRODROM
					MYOTONIC DYSTROPHY KINASE-RELATED CDC42-BINDING KINASE PHORBOLESTER BINDING PD075023: E630-N713	BLAST_PRODROM
					PHORBOLESTER BINDING KINASE DYSTROPHY KINASE-RELATED CDC42-BINDING SIMILAR SERINE/THREONINE PROTEIN GENGHIS KHAN PD150840: W1518-S1642	BLAST_PRODROM
					PHORBOLESTER BINDING DYSTROPHY KINASE-RELATED CDC42-BINDING KINASE GENGHIS KHAN MYOTONIC MYOTONIC PD011252: D833-P967	BLAST_PRODROM

Table 3

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
19 cont					PROTEIN KINASE DOMAIN DM00004;  Q09013 83-336: I79-Q331;  S42867 75-498: I79-L226, V238-Y404, P1653-D1728;  I38133 90-369: E78-L226, V238-G330;  P53894 353-658: L80-G221, D205-Q331	BLAST_DOMO
					Leucine zipper pattern L772-L793 L779-L800 L786-L807	MOTIFS
					C-type lectin domain signature C1067-C1088	MOTIFS
					Phorbol esters / diacylglycerol binding domain H1051-C1100	MOTIFS
					Protein kinases ATP-binding region signature I83-K106	MOTIFS
					Serine/Threonine protein kinases active-site signature Y197-M209	MOTIFS
20	3566882CD1	720	S91 S117 S146 S148 S264 S268 S299 S690 S697 T17 T166 T398 Y314		Ank repeat: E448-R480, D382-R414, V580-Q612, E415-A447, N481-Q513, S349-E381, Q547-A579, S613-K645, V646-G678	HMMER_PFAM
					Eukaryotic protein kinase domain: S156-P231	HMMER_PFAM
					Transmembrane domain: S146-Y171	TMAP
					Tyrosine kinase catalytic domain signature PR00109: M94-S107, L152-L174, E211-F233	BLIMPS_PRINTS

Table 4

Polynucleotide SEQ ID NO./ Incyte ID/ Sequence Length	Sequence Fragments
21/4615110CB1/5200	1-224, 1-277, 4-272, 14-161, 14-225, 42-679, 43-503, 43-609, 43-708, 43-714, 43-872, 48-688, 124-438, 178-4215, 199-420, 200-720, 240-549, 352-679, 355-637, 355-756, 371-754, 374-992, 446-992, 459-1093, 506-1102, 545-827, 564-824, 763-1296, 825-1296, 869-1286, 869-1296, 870-1296, 958-1636, 1046-1625, 1049-1527, 1063-1697, 1098-1689, 1103-1299, 1103-1774, 1133-1736, 1250-1743, 1250-1768, 1250-1840, 1312-1857, 1376-1857, 1416-1857, 1426-1857, 1429-1857, 1496-2036, 1508-1998, 1515-2107, 1554-2211, 1635-2249, 1713-2241, 1716-2315, 1728-2380, 1775-2322, 1796-2438, 1809-2049, 2006-5055, 2020-2679, 2029-2385, 2056-2732, 2069-2702, 2107-2752, 2186-2443, 2196-2638, 2231-2580, 2232-2698, 2271-2775, 2287-2580, 2302-2741, 2335-2806, 2407-2857, 2409-2669, 2432-2980, 2796-2997, 2799-2997, 2810-3016, 2824-2994, 2950-3400, 3029-3604, 3029-3684, 3064-3648, 3100-3372, 3139-3684, 3186-3766, 3194-3457, 3212-3473, 3219-3456, 3228-3737, 3234-3704, 3236-3485, 3236-3719, 3245-3503, 3273-3839, 3273-3887, 3295-3689, 3317-3583, 3317-3604, 3317-3939, 3341-3634, 3351-3979, 3357-3615, 3375-3621, 3396-3971, 3428-4081, 3454-4092, 3475-4060, 3479-4086, 3488-4156, 3491-3759, 3511-3828, 3511-3977, 3540-3825, 3540-3985, 3540-4047, 3548-3834, 3550-4216, 3580-3916, 3590-3928, 3599-4202, 3611-4211, 3627-4351, 3629-4099, 3629-4339, 3630-3907, 3630-4382, 3634-4382, 3641-4215, 3645-3920, 3649-3932, 3649-3933, 3650-3889, 3651-3904, 3654-4181, 3654-4215, 3660-4212, 3662-4080, 3664-4226, 3667-4162, 3667-4210, 3672-4212, 3675-4215, 3683-4211, 3693-4230, 3704-4211, 3706-4173, 3712-4215, 3728-4215, 3729-4215, 3730-4214, 3735-4214, 3737-4112, 3748-4213, 3752-4575, 3755-4025, 3766-4216, 3770-4382, 3771-4382, 3774-4215,

Table 4

Polynucleotide SEQ ID NO./ Incye ID/ Sequence Length	Sequence Fragments
	3776-4192, 3781-4216, 3782-4215, 3784-4215, 3786-4023, 3786-4216, 3791-4211, 3793-4211, 3796-4215, 3796-4216, 3805-4090, 3805-4164, 3807-4164, 3808-4215, 3809-4197, 3810-4144, 3817-4215, 3821-4112, 3821-4152, 3833-4162, 3835-4084, 3843-4103, 3850-4145, 3852-4205, 3852-4215, 3854-4442, 3858-4165, 3863-4121, 3876-4442, 3884-4139, 3885-4382, 3888-4216, 3905-4380, 3941-4382, 3947-4215, 4013-4562, 4081-4243, 4171-4645, 4178-4610, 4194-4692, 4194-4697, 4194-4698, 4194-4699, 4194-4749, 4194-4780, 4194-4904, 4194-4933, 4207-4496, 4208-4470, 4208-4486, 4208-4492, 4208-4493, 4208-4496, 4208-4525, 4208-4644, 4208-4680, 4208-4683, 4208-4687, 4208-4691, 4208-4694, 4208-4702, 4208-4707, 4210-4526, 4211-4496, 4211-4680, 4215-4496, 4216-4496, 4217-4480, 4222-4496, 4241-4382, 4241-4496, 4243-4629, 4252-4612, 4257-4522, 4257-4534, 4257-4541, 4257-4542, 4257-4545, 4257-4562, 4291-4707, 4292-4575, 4298-4605, 4298-4771, 4304-4549, 4304-4659, 4304-4837, 4310-4709, 4310-4711, 4323-4580, 4342-5179, 4363-4639, 4363-5016, 4364-4642, 4364-4916, 4383-4647, 4399-4664, 4410-4663, 4410-4670, 4422-4681, 4429-4677, 4439-4715, 4442-5010, 4452-4699, 4453-5005, 4454-5025, 4484-5200, 4495-4669, 4495-4686, 4495-4691, 4495-4696, 4495-4697, 4496-4762, 4500-5187, 4502-5200, 4510-4749, 4511-4768, 4517-5200, 4521-5200, 4530-5185, 4537-5200, 4551-5183, 4575-4860, 4588-4844, 4591-4866, 4598-5157, 4605-5200, 4619-5197, 4626-5200, 4637-4904, 4647-5200, 4666-5190, 4679-5191, 4682-5200, 4701-5200, 4703-4958, 4707-4961, 4716-4959, 4716-4999, 4719-4946, 4725-4965, 4732-4999, 4736-5021, 4738-4989, 4753-5200, 4757-5013, 4758-5200, 4780-5200, 4794-5200, 4797-5200, 4799-5192, 4806-5135, 4808-5108, 4815-4988, 4819-5088, 4842-5200, 4844-5200, 4848-5200, 4853-5200, 4854-5200, 4858-5200, 4859-5200, 4893-5200, 4904-5200, 4909-5200, 4928-5200, 4945-5200, 4946-5200, 4950-5200, 4956-5200, 4971-5200, 4972-5200, 4973-5200, 4976-5200, 4979-5200, 4980-5178, 4980-5199, 4980-5200, 4984-5200, 4985-5200, 4986-5200, 4989-5200, 4994-5200, 4996-5200, 4998-5200, 5007-5200, 5008-5200, 5010-5200, 5011-5200, 5017-5200, 5028-5200, 5033-5200, 5034-5200, 5046-5200, 5053-5200, 5055-5200, 5093-5200, 5154-5200

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Table 4

Polynucleotide SEQ ID NO./ Incye ID/ Sequence Length	Sequence Fragments
22/4622229CBI/4330	<p>1-300, 1-484, 24-275, 101-700, 299-820, 301-964, 315-925, 414-1033, 419-994, 516-1036, 612-884, 764-1443, 792-1443, 978-1595, 992-1545, 999-1687, 1037-1301, 1192-1430, 1216-1495, 1222-1799, 1279-1779, 1357-1615, 1428-1746, 1429-1793, 1464-1655, 1464-1684, 1495-1880, 1529-2265, 1575-2005, 1629-2219, 1678-1992, 1714-2170, 1744-2317, 1819-1946, 1912-2384, 1933-2610, 1940-2459, 1960-2540, 1968-2426, 2009-2522, 2055-2660, 2100-2591, 2116-2640, 2131-2638, 2138-2479, 2149-2475, 2152-2750, 2153-2822, 2157-2700, 2191-2517, 2285-2439, 2301-2559, 2306-2520, 2307-2542, 2378-2872, 2411-2699, 2443-2997, 2533-3044, 2546-2787, 2546-3136, 2689-2945, 2709-2985, 2733-3001, 2734-2972, 2734-3009, 2843-3050, 2918-3155, 2918-3182, 2918-3201, 2918-3214, 2918-3218, 2930-3512, 2937-3238, 2997-3246, 3003-3135, 3004-3532, 3019-3269, 3046-3295, 3058-3348, 3107-3358, 3114-3383, 3148-3416, 3236-3489, 3251-3489, 3251-3682, 3251-3802, 3275-3534, 3276-3517, 3282-3554, 3282-3557, 3294-3562, 3319-3572, 3340-3600, 3376-3644, 3387-3675, 3424-3662, 3450-3715, 3505-3728, 3524-3759, 3542-3825, 3552-4117, 3580-4260, 3590-4105, 3605-3731, 3607-3859, 3625-4321, 3634-4156, 3645-3871, 3645-4133, 3672-4313, 3677-4295, 3678-3918, 3684-3945, 3684-4124, 3694-4321, 3709-4317, 3715-4290, 3718-4311, 3733-4151, 3755-3919, 3786-4041, 3786-4044, 3786-4064, 3786-4255, 3786-4313, 3787-4076, 3791-4317, 3811-4329, 3814-4214, 3838-4082, 3839-4051, 3848-4100, 3848-4329, 3852-4315, 3853-4330, 3861-4328, 3877-4133, 3877-4134, 3877-4141, 3877-4330, 3879-4230, 3883-4329, 3885-4300, 3885-4329, 3886-4132, 3887-4329, 3888-4330, 3889-4328, 3890-4271, 3890-4329, 3898-4316, 3899-4330, 3901-4329, 3903-4321, 3903-4328, 3906-4329, 3907-4330, 3909-4330, 3910-4329, 3913-4330, 3914-4324, 3916-4247, 3916-4300, 3916-4328, 3916-4330, 3923-4329, 3923-4330, 3936-4051, 3936-4327, 3936-4330, 3940-4328, 3944-4329, 3965-4328, 3967-4203, 3990-4329, 3998-4329, 3999-4329, 4001-4329, 4010-4230, 4013-4330, 4026-4230, 4027-4230, 4027-4330, 4028-4328, 4030-4230, 4031-4230, 4031-4330, 4052-4229, 4052-4230, 4053-4328, 4053-4330, 4056-4329, 4061-4327, 4062-4329, 4066-4218, 4067-4329, 4068-4279, 4069-4330, 4082-4197, 4099-4328, 4099-4329, 4100-4330, 4109-4249, 4113-4329, 4156-4328</p>

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Table 4

Polynucleotide SEQ ID NO./ Incye ID/ Sequence Length	Sequence Fragments
23/72338203CB1/2851	1-557, 1-886, 238-885, 550-724, 718-1202, 726-885, 726-886, 736-1198, 774-885, 774-1041, 774-1145, 774-1200, 905-1196, 927-1169, 928-1431, 931-1516, 942-1251, 942-1347, 949-1235, 980-1452, 997-1452, 1002-1259, 1021-1312, 1038-1324, 1042-1522, 1049-1452, 1073-1452, 1085-1259, 1114-1319, 1114-1659, 1142-1259, 1157-1259, 1158-1259, 1174-1259, 1190-1463, 1190-1647, 1210-1295, 1238-1531, 1250-1496, 1259-1428, 1259-1457, 1259-1483, 1259-1538, 1261-1538, 1275-1573, 1290-1896, 1292-1587, 1372-1853, 1437-1689, 1440-1699, 1445-2001, 1446-1717, 1456-1483, 1456-1538, 1456-1603, 1461-1483, 1470-1719, 1470-2068, 1472-1673, 1472-2034, 1478-1711, 1512-1797, 1530-1661, 1533-1576, 1456-1603, 1461-1483, 1470-1719, 1470-2068, 1472-1673, 1732-1877, 1774-1894, 1793-1981, 1793-2297, 1838-1736, 1544-1786, 1575-1603, 1609-1898, 1669-2000, 1712-1983, 1732-1877, 1774-1894, 1793-1981, 1793-2297, 1838-2104, 1840-2189, 1843-2639, 1852-2120, 1869-2773, 1888-2221, 1890-2496, 1892-2624, 1904-2510, 1909-2108, 1909-2133, 1911-2454, 1929-2096, 1929-2544, 1941-2198, 1941-2624, 1942-2226, 1943-2214, 1945-2632, 1961-2628, 1966-2108, 1971-2227, 1975-2058, 1984-2068, 1987-2319, 1997-2287, 1997-2291, 1999-2469, 2002-2577, 2004-2799, 2032-2208, 2053-2544, 2063-2239, 2075-2109, 2110-2605, 2111-2639, 2117-2687, 2131-2751, 2132-2808, 2140-2481, 2673, 2053-2544, 2063-2239, 2075-2109, 2110-2605, 2111-2639, 2117-2687, 2131-2751, 2132-2808, 2140-2481, 2144-2741, 2146-2695, 2156-2359, 2176-2469, 2184-2816, 2188-2687, 2201-2453, 2202-2815, 2205-2683, 2208-2682, 2209-2764, 2211-2834, 2215-2575, 2215-2771, 2227-2784, 2228-2795, 2228-2844, 2229-2626, 2231-2551, 2232-2632, 2245-2499, 2250-2814, 2272-2725, 2272-2757, 2275-2829, 2282-2532, 2282-2580, 2282-2738, 2282-2815, 2282-2839, 2283-2587, 2295-2742, 2305-2562, 2305-2669, 2310-2552, 2315-2704, 2319-2550, 2324-2565, 2331-2824, 2337-2851, 2354-2601, 2355-2533, 2356-2851, 2360-2779, 2368-2824, 2372-2826, 2373-2824, 2374-2822, 2375-2684, 2376-2830, 2378-2626, 2379-2831, 2381-2824, 2386-2824, 2388-2824, 2395-2828, 2399-2771, 2402-2824, 2402-2833, 2406-2828, 2418-2818, 2418-2829, 2427-2702, 2432-2710, 2437-2700, 2452-2824
24/4885040CB1/2361	1-426, 20-113, 361-537, 410-605, 410-773, 410-832, 410-894, 410-915, 410-919, 410-983, 410-988, 410-1030, 420-1060, 430-819, 458-848, 488-1093, 682-1293, 728-1328, 735-1165, 753-1063, 985-1072, 986-1601, 1132-1757, 1191-1641, 1201-1845, 1202-1733, 1241-1721, 1313-1857, 1378-1619, 1378-1874, 1384-1943, 1432-1895, 1522-1797, 1610-1902, 1722-2311, 1745-2323, 1792-2222, 1794-2184, 1797-2036, 1810-2061, 1812-2139, 1816-2361, 1833-2352, 1871-2361, 1903-2361

Table 4

Polynucleotide SEQ ID NO./ Incyte ID/ Sequence Length	Sequence Fragments
25/7484507CB1/2285	1-262, 10-408, 16-408, 76-325, 93-408, 109-285, 109-290, 109-293, 109-323, 109-537, 109-541, 109-548, 109-582, 109-590, 110-281, 110-285, 110-290, 112-281, 112-285, 112-544, 119-590, 414-777, 414-2004, 499-590, 526-590, 776-1001, 776-1060, 906-1060, 913-1060, 953-1060, 967-1060, 1408-1964, 1409-2045, 1410-1946, 1413-1949, 1450-1500, 1463-2003, 1489-2121, 1504-2003, 1511-1616, 1512-2037, 1526-2216, 1530-2059, 1575-2117, 1593-2260, 1596-2255, 1632-2261, 1685-2142, 1685-2145, 1708-2257, 1730-2238, 1730-2263, 1790-2261, 1818-2263, 1830-2263, 1835-2223, 1835-2283, 1835-2284, 1835-2285, 1837-2256, 1839-2285, 1845-2285
26/7198931CB1/4858	1-189, 59-4745, 429-469, 484-949, 499-637, 500-896, 502-884, 502-896, 633-743, 808-994, 808-1187, 810-1183, 888-1187, 1108-1468, 1108-1779, 1108-1813, 1108-1834, 1108-1853, 1108-1878, 1108-1888, 1110-1468, 1111-1834, 1141-1834, 1145-1834, 1166-1834, 1353-2083, 1362-2083, 1387-2092, 1391-1927, 1392-2083, 1399-2083, 1403-2044, 1407-2044, 1422-1893, 1425-2042, 1444-2092, 1504-2044, 1628-2092, 1852-2044, 1894-2439, 2099-2690, 2121-2632, 2267-2715, 2382-3037, 2382-3046, 2382-3127, 2652-2880, 3173-3755, 3270-3734, 3327-3623, 3349-4153, 3392-4150, 3534-4063, 3534-4255, 3592-3774, 3592-4210, 3805-4436, 3828-4523, 3896-4167, 3898-4377, 3898-4564, 3920-4557, 3933-4577, 3945-4194, 3959-4214, 3979-4273, 3991-4591, 4036-4172, 4112-4254, 4113-4311, 4113-4500, 4114-4254, 4192-4450, 4215-4858, 4257-4326
27/7482905CB1/2903	1-607, 266-444, 363-941, 406-1048, 438-711, 459-1020, 497-607, 502-851, 536-607, 570-711, 710-918, 710-922, 710-931, 774-941, 867-1100, 869-1525, 870-1150, 879-1447, 962-1227, 969-1100, 974-1583, 1100-1699, 1300-1767, 1304-1767, 1333-1616, 1394-1684, 1394-2033, 1434-1944, 1434-2021, 1466-1642, 1591-1879, 1725-1996, 1746-2126, 1847-2508, 1935-2183, 2073-2183, 2091-2459, 2091-2643, 2091-2648, 2186-2666, 2350-2616, 2350-2903, 2365-2856, 2367-2663, 2435-2677, 2435-2808
28/7483019CB1/1812	1-235, 20-323, 22-235, 154-235, 154-321, 194-991, 196-823, 196-883, 196-900, 196-901, 196-903, 196-906, 196-913, 196-914, 196-919, 196-938, 196-940, 196-945, 196-966, 196-967, 196-973, 196-983, 196-996, 196-1014, 201-948, 236-321, 236-323, 322-590, 421-573, 487-1202, 487-1247, 487-1249, 487-1284, 487-1292, 487-1324, 550-1321, 568-1321, 574-1321, 586-1273, 590-655, 591-1321, 597-1321, 600-1321, 603-1321, 607-1321, 611-1321, 612-1321, 622-1321, 625-1321, 628-1321, 634-1321, 662-1321, 674-1321, 680-1282, 692-1321, 703-1321, 728-1282, 728-1285, 728-1287, 729-1287, 730-1287, 745-1285, 794-869, 795-1287, 827-1285, 854-1287, 950-1043, 950-1152, 985-1287, 1044-1287, 1151-1219, 1151-1285, 1151-1287, 1151-1689, 1153-1287, 1153-1482, 1159-1224, 1159-1421, 1159-1539, 1159-1638, 1159-1752, 1187-1287, 1187-1810, 1188-1812, 1238-1285, 1238-1287, 1287-1598, 1287-1635, 1287-1809, 1288-1482

Table 4

Polynucleotide SEQ ID NO./ Incye ID/ Sequence Length	Sequence Fragments
29/5455490CBI/5480	<p>1-689, 28-689, 373-686, 373-689, 413-867, 414-694, 414-715, 414-754, 414-843, 439-843, 448-1239, 508-843, 514-689, 529-843, 582-843, 597-843, 598-684, 598-689, 598-888, 598-994, 598-1070, 598-1081, 598-1176, 598-1230, 606-843, 610-867, 610-1172, 610-1237, 626-820, 634-1250, 715-1294, 723-1016, 723-1182, 767-1375, 796-1488, 910-1439, 920-1358, 969-1492, 982-1633, 1039-1581, 1056-1465, 1065-1334, 1065-1666, 1072-1435, 1098-1650, 1122-5330, 1129-1672, 1165-1318, 1204-1637, 1206-1459, 1206-1922, 1211-1485, 1244-1834, 1268-1874, 1274-1565, 1282-1907, 1284-1407, 1307-1749, 1312-1874, 1335-1884, 1340-1470, 1348-1562, 1406-1851, 1421-1625, 1444-1781, 1444-1927, 1557-2181, 1704-1965, 1710-2022, 1710-2260, 1723-2016, 1727-1947, 1785-2306, 1793-2282, 1805-2216, 1805-2244, 1944-2299, 1952-1985, 1953-2130, 1953-2235, 2067-2693, 2088-2746, 2105-2320, 2105-2586, 2105-2627, 2151-2380, 2152-2711, 2174-2711, 2263-2711, 2270-3062, 2284-3062, 2321-2876, 2349-3062, 2351-2957, 2357-2977, 2383-2960, 2383-3004, 2387-3159, 2389-3038, 2393-3059, 2404-3015, 2426-2804, 2449-2838, 2451-2987, 2453-2936, 2459-2908, 2461-2869, 2462-3139, 2464-3062, 2466-3070, 2483-2926, 2485-3017, 2492-3045, 2494-2712, 2494-2739, 2494-2940, 2504-2757, 2519-3062, 2526-3141, 2555-3179, 2565-3047, 2565-3085, 2565-3092, 2570-2773, 2579-2791, 2580-3023, 2597-3176, 2621-3045, 2626-3176, 2641-3044, 2659-2912, 2660-2945, 2660-2958, 2665-2931, 2666-2931, 2675-3333, 2740-3115, 2743-2824, 2752-3027, 2753-2977, 2754-3031, 2766-3182, 2781-3328, 2798-3012, 2807-2985, 2866-3078, 2883-3205, 2886-3032, 2902-3151, 2915-3092, 2923-3119, 2923-3120, 2924-3102, 2926-3120, 2929-3205, 2930-3125, 2955-3069, 2956-3584, 3002-3120, 3037-3637, 3057-3205, 3073-3719, 3082-3205, 3108-3749, 3108-3783, 3119-3576, 3131-3717, 3141-3671, 3156-3337, 3194-3496, 3217-3372, 3228-3544, 3254-3611, 3261-3507, 3266-3652, 3266-3766, 3266-3801, 3270-3658, 3286-3913, 3292-3488, 3298-3847, 3301-3586, 3301-3642, 3329-3962, 3347-3538, 3351-3546, 3353-3596, 3353-3850, 3353-3869, 3356-3626, 3361-3606, 3363-3605, 3364-3921, 3374-3989, 3388-3996, 3393-3990, 3423-3733, 3424-3906, 3426-4005, 3443-3563, 3443-3633, 3443-3717, 3443-3801, 3456-3715, 3457-3846, 3459-3965, 3460-3782, 3460-3882, 3460-3935, 3472-3726, 3481-3801, 3521-4146, 3529-3932, 3532-3965, 3533-3833, 3577-4095, 3657-3801, 3686-4203, 3705-3974, 3722-4164, 3724-4107, 3724-4157, 3732-4019, 3746-4376,</p>

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Table 4

Polynucleotide SEQ ID NO./ Incyte ID/ Sequence Length	Sequence Fragments
	<p>3785-3954, 3800-4054, 3807-4090, 3811-4093, 3814-4088, 3825-4115, 3826-4341, 3827-4467, 3829-3936, 3829-4354, 3844-4075, 3875-4086, 3875-4361, 3891-4548, 3901-3987, 3954-4219, 3967-4299, 3987-4614, 4001-4639, 4004-4281, 4011-4175, 4021-4129, 4021-4296, 4026-4177, 4035-4305, 4035-4547, 4041-4120, 4044-4182, 4044-4330, 4047-4592, 4048-4382, 4048-4387, 4048-4711, 4077-4494, 4088-4256, 4088-4286, 4088-4311, 4088-4323, 4088-4331, 4088-4384, 4088-4450, 4088-4466, 4088-4472, 4088-4473, 4088-4482, 4088-4510, 4088-4530, 4091-4492, 4099-4707, 4109-4419, 4111-4335, 4111-4536, 4112-4767, 4115-4379, 4121-4991, 4125-4720, 4128-4762, 4144-4790, 4151-4594, 4156-4622, 4161-4404, 4161-4576, 4164-4396, 4164-4421, 4170-4428, 4173-4684, 4173-4781, 4178-4743, 4180-4415, 4180-4417, 4183-4531, 4188-4455, 4204-4449, 4211-4826, 4213-4422, 4239-4849, 4240-4570, 4244-4333, 4250-4732, 4250-5021, 4250-5047, 4256-4385, 4264-4526, 4265-4590, 4267-4628, 4269-4587, 4283-4887, 4293-4546, 4297-4446, 4297-4752, 4301-4743, 4303-4605, 4311-4634, 4311-4640, 4311-4649, 4316-4771, 4317-4633, 4325-4715, 4334-4986, 4343-4598, 4343-4900, 4345-4933, 4358-4660, 4359-4743, 4361-4667, 4387-4836, 4395-4845, 4418-4678, 4421-5005, 4423-5012, 4431-4698, 4431-4709, 4431-4865, 4433-4782, 4433-5002, 4436-4816, 4439-4584, 4457-5346, 4458-5128, 4463-4723, 4464-4995, 4469-5095, 4478-4974, 4485-5050, 4489-4766, 4491-4772, 4517-5333, 4525-4868, 4530-4715, 4530-5009, 4530-5214, 4534-4970, 4536-5140, 4541-4995, 4541-5049, 4541-5153, 4547-4796, 4548-4819, 4551-5007, 4551-5013, 4551-5028, 4553-4846, 4574-4878, 4587-4818, 4596-4843, 4616-4924, 4616-5049, 4626-5314, 4630-4830, 4630-5177, 4637-4827, 4641-5151, 4646-4847, 4674-5333, 4703-5359, 4709-5376, 4720-5333, 4727-5374, 4745-5283, 4630-5177, 4637-4827, 4641-5151, 4646-4847, 4674-5333, 4703-5359, 4709-5376, 4720-5333, 4727-5374, 4745-5283, 4747-5387, 4754-5376, 4754-5386, 4773-5294, 4786-5333, 4791-5385, 4799-5480, 4806-5376, 4817-5385, 4817-5388, 4822-5378, 4838-5383, 4843-5388, 4857-5372, 4859-5374, 4874-5312, 4876-5349, 4876-5385, 4877-5345, 4888-5373, 4901-5324, 4904-5386, 4909-5379, 4913-5338, 4914-5386, 4918-5385, 4923-5386, 4923-5388, 4932-5386, 4936-5388, 4940-5386, 4962-5362, 4962-5386, 4968-5339, 4968-5376, 4968-5385, 4968-5392, 4970-5385, 4972-5386, 4975-5388, 4980-5476, 4981-5388, 5000-5386, 5004-5300, 5004-5342, 5004-5385, 5005-5293, 5009-5385, 5016-5386, 5032-5386, 5039-5307, 5046-5360, 5048-5386, 5053-5385, 5061-5385, 5061-5388, 5073-5368, 5077-5339, 5080-5386, 5092-5385, 5098-5366, 5099-5387, 5100-5385, 5104-5385, 5121-5364, 5123-5369, 5123-5387, 5129-5386, 5129-5387, 5136-5338, 5136-5376, 5136-5385, 5136-5386, 5141-5352, 5143-5386, 5145-5388, 5148-5386, 5154-5385, 5154-5386, 5162-5386, 5163-5388, 5194-5386, 5198-5385, 5203-5385, 5207-5382, 5211-5386, 5217-5385, 5240-5388, 5259-5385, 5264-5382, 5264-5387, 5267-5385, 5279-5386, 5286-5381, 5286-5386</p>

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Table 4

Polynucleotide SEQ ID NO./ Incyte ID/ Sequence Length	Sequence Fragments
30/5547067CB1/1568	1-372, 1-382, 1-386, 4-386, 5-382, 5-384, 5-386, 7-386, 11-385, 24-386, 60-386, 66-386, 67-386, 87-386, 116-386, 127-386, 136-386, 158-454, 170-386, 312-632, 387-458, 387-546, 387-547, 387-561, 387-584, 387-585, 387-598, 387-632, 387-674, 387-701, 387-729, 387-757, 387-785, 387-855, 387-859, 387-862, 387-873, 387-882, 387-883, 388-585, 388-883, 391-841, 391-883, 417-632, 436-883, 553-883, 564-1066, 717-785, 722-997, 722-1208, 770-1029, 1052-1568, 1120-1146, 1120-1161, 1120-1163, 1120-1206, 1120-1208, 1121-1208, 1209-1312, 1236-1317, 1320-1561, 1320-1568
31/71675660CB1/2365	1-505, 2-540, 20-479, 67-732, 162-239, 198-505, 224-660, 267-529, 305-540, 376-897, 390-977, 431-1088, 448-1007, 528-1183, 540-1091, 565-931, 611-1271, 635-1150, 648-1187, 666-826, 694-1334, 696-1390, 698-868, 727-1316, 794-1494, 813-1423, 850-1066, 860-1482, 875-1530, 884-1146, 895-1239, 955-1649, 978-1215, 980-1470, 1007-1545, 1027-1669, 1036-1526, 1036-1532, 1045-1593, 1062-1638, 1068-1630, 1068-1665, 1143-1679, 1155-1681, 1166-1822, 1175-1595, 1177-1797, 1340-2015, 1459-1757, 1526-1827, 1535-1865, 1621-2243, 1628-2243, 1733-2001, 1900-2361, 1903-2351, 1916-2355, 1929-2362, 1934-2102, 1941-2243, 1956-2365, 2004-2364, 2005-2358, 2170-2364
32/71678683CB1/2626	1-505, 2-540, 67-732, 198-505, 224-660, 305-540, 376-897, 431-1088, 448-1007, 528-1183, 565-931, 611-1271, 635-1150, 648-1187, 666-826, 694-1334, 696-1390, 698-868, 727-1316, 794-1494, 813-1423, 850-1066, 860-1482, 875-1530, 884-1146, 895-1239, 955-1649, 979-1215, 980-1470, 1007-1545, 1027-1669, 1036-1526, 1036-1532, 1045-1593, 1062-1638, 1068-1306, 1068-1547, 1068-1630, 1143-1679, 1155-1681, 1166-1822, 1175-1595, 1177-1797, 1364-1970, 1397-1892, 1459-1757, 1490-2081, 1623-2284, 1638-2233, 1657-2346, 1709-2276, 1810-2103, 1904-2310, 1927-2350, 1963-2341, 2002-2362, 2039-2446, 2045-2264, 2055-2351, 2086-2362, 2171-2626, 2228-2350
33/7474567CB1/3961	1-45, 1-780, 1-784, 1-795, 1-826, 1-847, 8-843, 44-495, 45-464, 153-854, 188-526, 215-870, 282-1131, 286-1131, 288-1131, 296-1131, 303-1131, 319-910, 319-975, 320-1131, 322-1131, 330-1124, 331-822, 350-1127, 561-870, 697-846, 801-1413, 869-1153, 879-1537, 895-1480, 1183-1827, 1217-1845, 1423-1950, 1499-2034, 1722-2344, 1770-2045, 1770-2383, 1801-2083, 1815-2058, 1942-2482, 1975-2115, 2006-2328, 2079-2335, 2079-2361, 2182-2416, 2182-2433, 2182-2651, 2260-2522, 2337-2590, 2420-2698, 2522-2746, 2523-2808, 2590-2994, 2680-2920, 2680-2932, 2684-3237, 2712-2990, 2727-2969, 2755-2995, 2814-3063, 2814-3082, 2869-3146, 2903-3147, 2903-3398, 2934-3172, 2966-3245, 2966-3250, 3060-3375, 3097-3380, 3144-3359, 3144-3438, 3182-3464, 3229-3476, 3229-3531, 3300-3584, 3312-3561, 3319-3954, 3344-3961, 3346-3587, 3359-3613, 3379-3641, 3426-3958, 3449-3639, 3449-3701

Table 4

Polynucleotide SEQ ID NO./ Incyte ID/ Sequence Length	Sequence Fragments
34/3838946CB1/2210	1-578, 65-574, 86-644, 137-536, 186-811, 219-513, 219-702, 240-465, 240-774, 240-811, 280-1851, 657-809, 689-1227, 711-1211, 768-1040, 777-1069, 807-1145, 812-1066, 818-1295, 847-1068, 915-1567, 915-1571, 945-1295, 1095-1361, 1095-1596, 1230-1708, 1324-1581, 1414-1953, 1446-1727, 1467-1748, 1469-1909, 1470-2130, 1560-1914, 1583-1896, 1585-2036, 1610-2182, 1615-2193, 1637-2206, 1638-1810, 1638-2195, 1644-2181, 1645-2168, 1660-2144, 1721-2210, 1733-2178, 1752-1888, 1764-2210, 1771-2076, 1815-2197, 1833-2103, 1839-2145, 1859-2125, 2001-2161
35/72001176CB1/4869	1-479, 53-662, 58-592, 241-462, 257-449, 272-519, 273-522, 288-515, 326-604, 346-597, 353-980, 361-626, 380-647, 397-637, 397-648, 407-652, 407-661, 410-664, 434-664, 498-664, 534-980, 804-1243, 804-1456, 804-1479, 927-1594, 988-1620, 989-1692, 1005-1712, 1023-1620, 1042-1628, 1074-1727, 1103-1712, 1134-1681, 1139-1832, 1187-1841, 1229-1743, 1274-1949, 1279-1978, 1306-1889, 1320-1915, 1358-1830, 1362-2392, 1403-1975, 1462-2010, 1566-2182, 1868-2595, 1961-2788, 2107-2953, 2131-2766, 2198-2343, 2198-2827, 2199-3008, 2244-2906, 2286-2869, 2308-2853, 2315-2983, 2315-3101, 2316-2903, 2325-2915, 2325-2989, 2357-3005, 2399-2903, 2402-2749, 2408-3224, 2410-2930, 2416-3025, 2433-3061, 2438-3059, 2448-3091, 2482-3141, 2498-3216, 2507-3110, 2510-3217, 2514-3181, 2516-3150, 2531-3231, 2538-3209, 2539-3234, 2547-3234, 2551-3042, 2555-3119, 2560-3319, 2561-3236, 2570-3186, 2573-3355, 2582-3167, 2582-3207, 2614-3163, 2617-2958, 2627-3197, 2630-3164, 2662-3068, 2672-3229, 2677-3217, 2682-3203, 2770-2914, 2858-3620, 2966-3770, 3112-3915, 3235-3980, 3241-3922, 3308-3991, 3350-4097, 3522-4032, 3658-3893, 4188-4662, 4193-4869
35 cont.	
36/55064363CB1/4480	1-642, 92-502, 478-1155, 503-666, 533-1344, 554-1344, 556-1344, 595-1113, 595-1170, 595-1203, 595-1210, 595-1213, 595-1239, 602-1252, 676-1102, 686-853, 687-841, 689-1344, 689-1398, 693-1127, 865-1391, 881-1584, 893-1330, 900-1459, 918-1679, 930-1656, 934-1635, 934-1660, 935-1562, 972-1441, 1001-1690, 1006-1517, 1019-1650, 1039-1344, 1049-1609, 1094-1421, 1100-1698, 1100-1722, 1100-1742, 1100-1837, 1103-1771, 1110-1454, 1135-1647, 1135-1828, 1171-1364, 1190-1667, 1221-1593, 1234-1752, 1248-1682, 1275-1949, 1295-2112, 1302-2112, 1316-2112, 1319-2112, 1329-2112, 1332-2112, 1345-2112, 1359-2112, 1403-2112, 1459-2025, 1459-2137, 1591-2392, 1599-2396, 1603-2388, 1607-2397, 1640-2396, 1641-2392, 1644-2397, 1646-2010, 1647-2108, 1647-2112, 1647-2396, 1665-2396, 1692-2187, 1701-2166, 1701-2289, 1701-2369, 1708-2112, 1708-2397, 1732-1889, 1732-1985, 1732-2112, 1781-2392, 1787-2610, 1790-2146, 1792-2146, 1794-2122, 1794-2228, 1817-2527, 1822-2201, 1839-2396, 1840-2396, 1843-2495, 1844-2504, 1856-2610, 1873-2610, 1964-2497, 1984-2497, 1984-2609, 1984-2610, 1987-2610, 2007-2497, 2015-2497, 2021-2532, 2044-2745, 2047-2738, 2065-2737, 2074-2497, 2096-2567, 2096-2589, 2096-2710,

Table 4

Polynucleotide SEQ ID NO./ Incye ID/ Sequence Length	Sequence Fragments
	2096-2729, 2096-2736, 2096-2769, 2114-2745, 2150-2793, 2153-2787, 2162-2883, 2175-2787, 2189-2810, 2225-2497, 2240-2883, 2247-2802, 2300-2979, 2315-2979, 2332-2962, 2332-2972, 2332-2975, 2332-2981, 2349-3040, 2363-2890, 2365-2802, 2390-2890, 2430-2890, 2431-2832, 2431-2862, 2431-2865, 2431-2877, 2431-2912, 2431-2917, 2431-2934, 2431-2946, 2431-2954, 2431-2961, 2431-2963, 2431-2964, 2431-2983, 2431-3012, 2431-3019, 2431-3021, 2431-3032, 2431-3036, 2431-3042, 2431-3043, 2431-3077, 2431-3081, 2431-3088, 2431-3092, 2431-3096, 2431-3105, 2431-3106, 2431-3112, 2431-3114, 2431-3135, 2431-3138, 2431-3150, 2431-3166, 2431-3213, 2431-3220, 2431-3247, 2432-3129, 2433-3018, 2433-3077, 2439-3016, 2440-3277, 2443-3272, 2452-3232, 2464-2564, 2467-3211, 2471-3331, 2481-3204, 2528-3084, 2534-3050, 2543-3140, 2545-3409, 2547-3003, 2551-2573, 2577-3158, 2578-3261, 2578-3325, 2603-3141, 2609-3435, 2625-3296, 2638-3102, 2642-3100, 2642-3304, 2644-3201, 2652-3310, 2661-3353, 2668-3243, 2697-3281, 2697-3412, 2700-3249, 2702-3295, 2713-3316, 2731-3243, 2731-3431, 2750-3502, 2757-3318, 2765-3299, 2768-3508, 2769-3435, 2771-3268, 2782-3326, 2784-3347, 2787-3461, 2798-3326, 2811-3703, 2818-3441, 2820-3277, 2832-3592, 2847-3563, 2850-3410, 2860-3442, 2861-3438, 2869-3445, 2882-3578, 2882-3608, 2882-3703, 2885-3558, 2909-3493, 2920-3505, 2922-3698, 2926-3505, 2928-3490, 2951-3452, 2952-3591, 2952-3742, 2954-3623, 2956-3537, 2960-3510, 2964-3516, 2965-3591, 2972-3426, 2972-3532, 2980-3528, 2989-3682, 2990-3583, 2993-3728, 2994-3764, 2995-3755, 2997-3776, 3006-3605, 3007-3587, 3014-3621, 3016-3624, 3031-3532, 3032-3547, 3062-3716, 3075-3396, 3075-3431, 3075-3437, 3075-3442, 3075-3479, 3075-3483, 3075-3587, 3075-3626, 3075-3645, 3082-3637, 3088-3691, 3091-3706, 3114-3754, 3140-3731, 3169-3692, 3185-3851, 3200-3768, 3219-3947, 3219-4035, 3232-3868, 3255-3926, 3276-4111, 3277-3854, 3280-3926, 3297-3948, 3303-3926, 3323-4150, 3334-4100, 3343-4047, 3373-4075, 3382-4047, 3391-4236, 3401-4234, 3405-4041, 3411-4036, 3412-3983, 3428-4086, 3430-4247, 3445-4047, 3467-4160, 3471-3963, 3476-3989, 3478-4056, 3480-3961, 3493-3965, 3508-4217, 3520-3991, 3534-4200, 3534-4290, 3538-3979, 3540-4209, 3551-4070, 3565-4249, 3580-4090, 3592-4072, 3606-3966, 3611-4118, 3616-4234, 3655-4315, 3672-4200, 3680-4207, 3696-4087, 3720-4228, 3738-4416, 3747-4169, 3756-4199, 3760-4279, 3783-4480, 3802-4277, 3805-4418, 3807-4313, 3834-4419, 3886-4224, 3896-4447, 3900-4480, 3907-4476, 3911-4480

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Table 4

Polynucleotide SEQ ID NO./ Incyte ID/ Sequence Length	Sequence Fragments
37/7482044CB1/4415	1-246, 1-460, 1-559, 1-669, 325-710, 385-719, 388-719, 456-716, 456-732, 456-1068, 516-719, 516-723, 549-719, 549-723, 587-1072, 643-1258, 686-1270, 716-1264, 805-1055, 805-1344, 805-1347, 805-1444, 805-1581, 864-1495, 960-1613, 993-1519, 1268-1816, 1305-2012, 1338-2003, 1438-1929, 1438-1980, 1438-1991, 1589-2102, 1864-2232, 1891-2477, 2015-2237, 2015-2667, 2079-2518, 2237-2516, 2237-2528, 2237-2529, 2237-2554, 2237-2560, 2237-2563, 2237-2564, 2237-2571, 2237-2574, 2237-2575, 2237-2604, 2237-2605, 2237-2624, 2237-2653, 2237-2678, 2237-2688, 2237-2693, 2237-2701, 2237-2717, 2237-2720, 2237-2730, 2237-2745, 2237-2753, 2237-2758, 2237-2770, 2237-2795, 2237-2803, 2237-2818, 2240-2510, 2240-2520, 2241-2688, 2241-2833, 2287-2863, 2290-2809, 2350-2846, 2404-2763, 2489-3189, 2513-3099, 2550-3188, 2589-2818, 2594-3281, 2604-2867, 2604-2886, 2604-2914, 2610-3232, 2612-2883, 2635-2886, 2644-3093, 2662-3238, 2701-3162, 2728-3227, 2772-3374, 2867-3472, 2889-3227, 2892-3628, 2905-3716, 2931-3606, 2937-3675, 2937-3699, 2947-3625, 2968-3645, 2990-3796, 2998-3725, 3010-3612, 3015-3648, 3023-3708, 3030-3516, 3031-3669, 3070-3653, 3083-3684, 3090-3797, 3136-3695, 3141-3768, 3165-3655, 3185-3727, 3187-4006, 3204-3852, 3204-3861, 3204-3877, 3204-3887, 3210-3861, 3212-3890, 3213-3856, 3220-3899, 3222-3695, 3226-3984, 3227-3889, 3256-3794, 3260-3715, 3265-4018, 3269-3986, 3274-3987, 3277-3817, 3277-3877, 3285-3878, 3304-3996, 3306-4011, 3316-3855, 3320-3914, 3334-3898, 3340-3900, 3343-3911, 3346-3727, 3348-4071, 3349-3995, 3367-3896, 3391-3916, 3393-3990, 3400-4086, 3425-3958, 3441-3947, 3479-4168, 3489-3990, 3494-4035, 3497-4105, 3504-4086, 3504-4096, 3515-4172, 3516-4172, 3517-3797, 3537-4145, 3539-4255, 3540-3943, 3540-3984, 3542-4171, 3542-4172, 3549-4348, 3562-4019, 3565-4153, 3583-4352, 3585-4122, 3585-4150, 3648-3995, 3653-4413, 3657-3981, 3667-4383, 3668-4327, 3677-4182, 3678-3995, 3711-4087, 3732-4286, 3738-4414, 3739-4354, 3740-4377, 3746-4398, 3746-4415, 3750-4392, 3776-3842, 3779-4415, 3808-4415, 3856-4415, 3863-4415, 3865-4415, 3895-4415, 3908-4415, 3917-4415, 3925-4415, 3972-4415
37 cont.	
38/7476595CB1/6306	1-829, 191-944, 191-950, 191-959, 191-964, 191-971, 192-488, 193-488, 223-488, 234-999, 244-488, 319-999, 398-999, 683-1074, 796-961, 796-1063, 961-6306, 962-1186, 1064-1186, 1064-1299, 1187-1299

Table 4

Polynucleotide SEQ ID NO./ Incyte ID/ Sequence Length	Sequence Fragments
39/71824382CB1/7151	1-525, 1-532, 188-467, 221-432, 266-533, 403-563, 435-718, 501-740, 585-1133, 594-876, 758-1034, 791-1005, 793-1247, 799-1047, 809-1248, 899-1172, 947-1206, 1077-1708, 1097-1737, 1172-1542, 1172-1583, 1260-1448, 1260-1748, 1283-1763, 1289-1744, 1309-1751, 1320-1744, 1341-1742, 1346-1706, 1385-1749, 1428-2103, 1457-1763, 1511-2109, 1530-2109, 1595-2109, 1612-1752, 1655-2102, 1655-2109, 1739-2109, 1924-2368, 1941-2109, 1946-2109, 1974-2526, 1979-2366, 1979-2642, 1980-2534, 2039-2274, 2039-2319, 2039-2536, 2039-2644, 2043-2109, 2148-2316, 2148-2335, 2148-2484, 2148-2542, 2148-2579, 2148-2588, 2148-2649, 2148-2753, 2148-2757, 2151-2757, 2156-2306, 2168-2413, 2202-2278, 2242-2889, 2243-2917, 2253-2609, 2284-2829, 2288-2829, 2326-2589, 2326-2934, 2326-2959, 2326-2975, 2388-3083, 2398-2526, 2445-2757, 2447-2757, 2503-3181, 2576-3079, 2581-2757, 2630-2740, 2634-3079, 2658-3181, 2704-2909, 2977-3181, 3102-3691, 3102-3769, 3104-3769, 3126-3181, 3333-3941, 3415-3943, 3452-3911, 3616-3912, 3616-4100, 3634-4171, 3634-4205, 3693-4292, 3890-4478, 3976-4399, 3976-4654, 4023-4452, 4090-4498, 4156-4417, 4202-4705, 4254-4915, 4254-4945,
	4303-4705, 4431-4984, 4513-5252, 4548-5253, 4613-4854, 4822-5203, 4885-5133, 4901-5173, 4901-5554, 4905-5581, 4968-5531, 4980-5438, 5006-5562, 5022-5182, 5028-5697, 5044-5663, 5061-5737, 5063-5562, 5064-5562, 5125-5430, 5154-5300, 5225-5505, 5293-5602, 5332-5781, 5335-5590, 5397-5697, 5409-5913, 5453-5715, 5507-5701, 5518-6120, 5569-6181, 5647-6231, 5667-6078, 5716-5948, 5806-6163, 5906-6157, 5906-6536, 6047-6292, 6147-6420, 6175-6590, 6176-6467, 6238-6447, 6238-7024, 6254-6429, 6269-6560, 6284-6600, 6397-6655, 6397-6973, 6423-7036, 6471-6717, 6497-7118, 6497-7125, 6521-7122, 6629-7087, 6643-6908, 6657-7116, 6820-7062, 6820-7124, 6820-7151, 6829-7077, 6838-7069, 6901-7136
40/3566882CB1/2378	1-219, 54-238, 54-571, 517-1197, 517-1241, 695-1241, 757-2216, 1241-1477, 1241-1534, 1241-1706, 1241-1779, 1241-1810, 1241-1812, 1241-1835, 1241-1846, 1241-1864, 1241-1873, 1242-1794, 1347-2004, 1372-1910, 1376-1881, 1488-1808, 1519-2155, 1542-2088, 1573-2221, 1576-2112, 1615-2026, 1618-2182, 1624-2139, 1641-2155, 1645-2316, 1652-2139, 1711-2218, 1717-1968, 1767-2370, 1785-2378, 1826-2367, 1844-2258, 1928-2143, 2032-2202, 2036-2206, 2304-2361

Table 5

Polynucleotide SEQ ID NO:	Incyte Project ID:	Representative Library
21	4615110CB1	BRAYDIN03
22	4622229CB1	BRAINON01
23	72358203CB1	BRAITUT03
24	4885040CB1	ENDANOT01
25	7484507CB1	BRAIFEN08
26	7198931CB1	SYNORAB01
27	7482905CB1	BMARTXE01
28	7483019CB1	BMARTXT02
29	5455490CB1	HNT2AGT01
30	5547067CB1	BRAIFEE05
31	71675660CB1	TESTNOT17
32	71678683CB1	TESTNOT17
33	7474567CB1	UCMCNOT02
34	3838946CB1	NOSEDIN01
35	72001176CB1	THPINOT03
36	55064363CB1	BRAIFET02
37	7482044CB1	BRAUNOR01
39	71824382CB1	BRABDIR01
40	3566882CB1	LUNLTUE02

Table 6

Library	Vector	Library Description
BMARTXE01	pINCY	This 5' biased random primed library was constructed using RNA isolated from treated SH-SY5Y cells derived from a metastatic bone marrow neuroblastoma, removed from a 4-year-old Caucasian female (Schering AG). The medium was MEM/HAM'S F12 with 10% fetal calf serum. After reaching about 80% confluency cells were treated with 6-Hydroxydopamine (6-OHDA) at 100 microM for 8 hours.
BMARTXT02	pINCY	Library was constructed using RNA isolated from treated SH-SY5Y cell line derived from bone marrow neuroblastoma tumor cells removed from a 4-year-old Caucasian female. The cells were cultured in the presence of retinoic acid.
BRABDIR01	pINCY	Library was constructed using RNA isolated from diseased cerebellum tissue removed from the brain of a 57-year-old Caucasian male, who died from a cerebrovascular accident. Patient history included Huntington's disease, emphysema, and tobacco abuse.
BRAIFEE05	PCDNA2.1	This 5' biased random primed library was constructed using RNA isolated from brain tissue removed from a Caucasian male fetus who was stillborn with a hypoplastic left heart at 23 weeks' gestation.
BRAIFEN08	pINCY	This normalized fetal brain tissue library was constructed from 400 thousand independent clones from a fetal brain tissue library. Starting RNA was made from brain tissue removed from a Caucasian male fetus who was stillborn with a hypoplastic left heart at 23 weeks' gestation. The library was normalized in 2 rounds using conditions adapted from Soares et al., PNAS (1994) 91:9228 and Bonaldo et al., Genome Research (1996) 6:791, except that a significantly longer (48 hours/round) reannealing hybridization was used.
BRAIFET02	pINCY	Library was constructed using RNA isolated from brain tissue removed from a Caucasian male fetus, who was stillborn with a hypoplastic left heart at 23 weeks' gestation.
BRAINON01	PSPORT1	Library was constructed and normalized from 4.88 million independent clones from the BRAINOT03 library. RNA was made from brain tissue removed from a 26-year-old Caucasian male during cranioplasty and excision of a cerebral meningeal lesion. Pathology for the associated tumor tissue indicated a grade 4 oligoastrocytoma in the right fronto-parietal part of the brain.
BRAITUT03	PSPORT1	Library was constructed using RNA isolated from brain tumor tissue removed from the left frontal lobe of a 17-year-old Caucasian female during excision of a cerebral meningeal lesion. Pathology indicated a grade 4 fibrillary giant and small-cell astrocytoma. Family history included benign hypertension and cerebrovascular disease.

Table 6

Library	Vector	Library Description
BRAUNOR01	pINCY	This random primed library was constructed using RNA isolated from striatum, globus pallidus and posterior putamen tissue removed from an 81-year-old Caucasian female who died from a hemorrhage and ruptured thoracic aorta due to atherosclerosis. Pathology indicated moderate atherosclerosis involving the internal carotids, bilaterally; microscopic infarcts of the frontal cortex and hippocampus; and scattered diffuse amyloid plaques and neurofibrillary tangles, consistent with age. Grossly, the leptomeninges showed only mild thickening and hyalinization along the superior sagittal sinus. The remainder of the leptomeninges was thin and contained some congested blood vessels. Mild atrophy was found mostly in the frontal poles and lobes, and temporal lobes, bilaterally. Microscopically, there were pairs of Alzheimer type II astrocytes within the deep layers of the neocortex. There was increased satellitosis around neurons in the deep gray matter in the middle frontal cortex. The amygdala contained rare diffuse plaques and neurofibrillary tangles. The posterior hippocampus contained a microscopic area of cystic cavitation with hemosiderin laden macrophages surrounded by reactive gliosis. Patient history included sepsis, cholangitis, post-operative atelectasis, pneumonia CAD, cardiomegaly due to left ventricular hypertrophy, splenomegaly, arteriolonephrosclerosis, nodular colloidal goiter, emphysema, CHF, hypothyroidism, and peripheral vascular disease.
BRAYDIN03	pINCY	This normalized library was constructed from 6.7 million independent clones from a brain tissue library. Starting RNA was made from RNA isolated from diseased hypothalamus tissue removed from a 57-year-old Caucasian male who died from a cerebrovascular accident. Patient history included Huntington's disease and emphysema. The library was normalized in 2 rounds using conditions adapted from Soares et al., PNAS (1994) 91:9228 and Bonaldo et al., Genome Research (1996) 6:791, except that a significantly longer (48 -hours/round) reannealing hybridization was used. The library was linearized and recircularized to select for insert containing clones.
ENDANOT01	PBLUESCRIPT	Library was constructed using RNA isolated from aortic endothelial cell tissue from an explanted heart removed from a male during a heart transplant.
HNT2AGT01	PBLUESCRIPT	Library was constructed at Stratagene (STR937233), using RNA isolated from the hNT2 cell line derived from a human teratocarcinoma that exhibited properties characteristic of a committed neuronal precursor. Cells were treated with retinoic acid for 5 weeks and with mitotic inhibitors for two weeks and allowed to mature for an additional 4 weeks in conditioned medium.

Table 6

Library	Vector	Library Description
LUNLTUE02	PCDNA2.1	This 5' biased random primed library was constructed using RNA isolated from left upper lobe lung tumor tissue removed from a 56-year-old Caucasian male during complete pneumonectomy, pericardectomy and regional lymph node excision. Pathology indicated grade 3 squamous cell carcinoma forming a mass in the left upper lobe centrally. The tumor extended through pleura into adjacent pericardium. Patient history included hemoptysis and tobacco abuse. Family history included benign hypertension, cerebrovascular accident, atherosclerotic coronary artery disease in the mother; prostate cancer in the father; and type II diabetes in the sibling(s).
NOSEDIN01	pINCY	This normalized nasal polyp tissue library was constructed from 1.08 million independent clones from a pooled nasal polyp tissue library. Starting RNA was made from pooled cDNA from two donors. cDNA was generated using mRNA isolated from a nasal polyp removed from a 78-year-old Caucasian male during nasal polypectomy (donor A) and from nasal polyps from another donor (donor B). Pathology (A) indicated a nasal polyp and striking eosinophilia, especially deep in the epithelium. In many instances, eosinophils were undergoing frank necrosis with striking deposition of Charcot-Leyden crystals. Foci of eosinophil infiltration in small islands of cells were seen in certain areas, and those areas closer to the appearance surface were losing definition and evidently undergoing necrosis. Examination of respiratory epithelium showed loss of surface epithelium in many areas, and there was a tendency for cells to aggregate around the epithelium. This nasal polyp showed typical histology for polypoid change associated with allergic disease. Patient history included asthma, allergy tests (which were positive for histamine but negative for common substances), a pulmonary function test (PFT, which showed reduction in the forced expiratory volume (FEV), with increase after use of a bronchodilator), and nasal polyps. Patient history (A) included asthma. Previous surgery (A) included a nasal polypectomy. The patient was not using glucocorticoids in treatment for asthma. The library was normalized in 1 round using conditions adapted from Soares et al., PNAS (1994) 91:9228-9232 and Bonaldo et al., Genome Research 6 (1996):791, except that a significantly longer (48 hours/round) reannealing hybridization was used.
SYNORAB01	PBLUESCRIPT	Library was constructed using RNA isolated from the synovial membrane tissue of a 68-year-old Caucasian female with rheumatoid arthritis.

Table 6

Library	Vector	Library Description
TESTNOT17	pINCY	Library was constructed from testis tissue removed from a 26-year-old Caucasian male who died from head trauma due to a motor vehicle accident. Serologies were negative. Patient history included a hernia at birth, tobacco use (1 1/2 ppd), marijuana use, and daily alcohol use (beer and hard liquor).
THPINOT03	pINCY	Library was constructed using RNA isolated from untreated THP-1 cells. THP-1 is a human promonocyte line derived from the peripheral blood of a 1-year-old Caucasian male with acute monocytic leukemia (ref: Int. J. Cancer (1980) 26:171).
UCMCNOT02	pINCY	Library was constructed using RNA isolated from mononuclear cells obtained from the umbilical cord blood of nine individuals.

Table 7

Program	Description	Reference	Parameter Threshold
ABI FACTURA	A program that removes vector sequences and masks ambiguous bases in nucleic acid sequences.	Applied Biosystems, Foster City, CA.	
ABI/PARACEL FDF	A Fast Data Finder useful in comparing and annotating amino acid or nucleic acid sequences.	Applied Biosystems, Foster City, CA; Paracel Inc., Pasadena, CA.	Mismatch <50%
ABI AutoAssembler	A program that assembles nucleic acid sequences.	Applied Biosystems, Foster City, CA.	
BLAST	A Basic Local Alignment Search Tool useful in sequence similarity search for amino acid and nucleic acid sequences. BLAST includes five functions: blastp, blastn, blastx, tblastn, and tblastx.	Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410; Altschul, S.F. et al. (1997) Nucleic Acids Res. 25:3389-3402.	ESTs: Probability value= 1.0E-8 or less Full Length sequences: Probability value= 1.0E-10 or less
FASTA	A Pearson and Lipman algorithm that searches for similarity between a query sequence and a group of sequences of the same type. FASTA comprises at least five functions: fasta, tfasta, fastx, tfastx, and ssearch.	Pearson, W.R. and D.J. Lipman (1988) Proc. Natl. Acad. Sci. USA 85:2444-2448; Pearson, W.R. (1990) Methods Enzymol. 183:63-98; and Smith, T.F. and M.S. Waterman (1981) Adv. Appl. Math. 2:482-489.	ESTs: fasta E value=1.06E-6 Assembled ESTs: fasta Identity= 95% or greater and Match length=200 bases or greater; fastx E value=1.0E-8 or less Full Length sequences: fastx score=100 or greater
BLIMPS	A BLocks IMProved Searcher that matches a sequence against those in BLOCKS, PRINTS, DOMO, PRODOM, and PFAM databases to search for gene families, sequence homology, and structural fingerprint regions.	Henikoff, S. and J.G. Henikoff (1991) Nucleic Acids Res. 19:6565-6572; Henikoff, J.G. and S. Henikoff (1996) Methods Enzymol. 266:88-105; and Attwood, T.K. et al. (1997) J. Chem. Inf. Comput. Sci. 37:417-424.	Probability value= 1.0E-3 or less
HMMER	An algorithm for searching a query sequence against hidden Markov model (HMM)-based databases of protein family consensus sequences, such as PFAM.	Krogh, A. et al. (1994) J. Mol. Biol. 235:1501-1531; Sonnhammer, E.L.L. et al. (1988) Nucleic Acids Res. 26:320-322; Durbin, R. et al. (1998) Our World View, in a Nutshell, Cambridge Univ. Press, pp. 1-350.	PFAM hits: Probability value= 1.0E-3 or less Signal peptide hits: Score= 0 or greater



Table 7 (cont.)

Program	Description	Reference	Parameter Threshold
ProfileScan	An algorithm that searches for structural and sequence motifs in protein sequences that match sequence patterns defined in Prosite.	Gribskov, M. et al. (1988) CABIOS 4:61-66; Gribskov, M. et al. (1989) Methods Enzymol. 183:146-159; Bairoch, A. et al. (1997) Nucleic Acids Res. 25:217-221.	Normalized quality score <sub>2</sub> GCG-specified 'HIGH' value for that particular Prosite motif. Generally, score=1.4-2.1.
Phred	A base-calling algorithm that examines automated sequencer traces with high sensitivity and probability.	Ewing, B. et al. (1998) Genome Res. 8:175-185; Ewing, B. and P. Green (1998) Genome Res. 8:186-194.	
Phrap	A Phils Revised Assembly Program including SWAT and CrossMatch, programs based on efficient implementation of the Smith-Waterman algorithm, useful in searching sequence homology and assembling DNA sequences.	Smith, T.F. and M.S. Waterman (1981) Adv. Appl. Math. 2:482-489; Smith, T.F. and M.S. Waterman (1981) J. Mol. Biol. 147:195-197; and Green, P., University of Washington, Seattle, WA.	Score= 120 or greater; Match length= 56 or greater
Consed	A graphical tool for viewing and editing Phrap assemblies.	Gordon, D. et al. (1998) Genome Res. 8:195-202.	
SPScan	A weight matrix analysis program that scans protein sequences for the presence of secretory signal peptides.	Nielson, H. et al. (1997) Protein Engineering 10:1-6; Claverie, J.M. and S. Audic (1997) CABIOS 12:431-439.	Score=3.5 or greater
TMAP	A program that uses weight matrices to delineate transmembrane segments on protein sequences and determine orientation.	Persson, B. and P. Argos (1994) J. Mol. Biol. 237:182-192; Persson, B. and P. Argos (1996) Protein Sci. 5:363-371.	
TMHMMER	A program that uses a hidden Markov model (HMM) to delineate transmembrane segments on protein sequences and determine orientation.	Sonnhammer, E.L. et al. (1998) Proc. Sixth Intl. Conf. on Intelligent Systems for Mol. Biol., Glasgow et al., eds., The Am. Assoc. for Artificial Intelligence Press, Menlo Park, CA, pp. 175-182.	
Motifs	A program that searches amino acid sequences for patterns that matched those defined in Prosite.	Bairoch, A. et al. (1997) Nucleic Acids Res. 25:217-221; Wisconsin Package Program Manual, version 9, page M51-59, Genetics Computer Group, Madison, WI.	

What is claimed is:

1. An isolated polypeptide selected from the group consisting of:
  - a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-20,
  - b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-20,
  - c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-20, and
  - d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-20.
2. An isolated polypeptide of claim 1 comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-20.
3. An isolated polynucleotide encoding a polypeptide of claim 1.
4. An isolated polynucleotide encoding a polypeptide of claim 2.
5. An isolated polynucleotide of claim 4 comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:21-40.
6. A recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide of claim 3.
7. A cell transformed with a recombinant polynucleotide of claim 6.
8. A transgenic organism comprising a recombinant polynucleotide of claim 6.
9. A method of producing a polypeptide of claim 1, the method comprising:
  - a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide, and said recombinant polynucleotide comprises a promoter sequence operably linked to a polynucleotide encoding the polypeptide of claim 1, and

b) recovering the polypeptide so expressed.

10. A method of claim 9, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NO:1-20.

5

11. An isolated antibody which specifically binds to a polypeptide of claim 1.

12. An isolated polynucleotide selected from the group consisting of:

10

a) a polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:21-40,

b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:21-40,

c) a polynucleotide complementary to a polynucleotide of a),

15

d) a polynucleotide complementary to a polynucleotide of b), and

e) an RNA equivalent of a)-d).

13. An isolated polynucleotide comprising at least 60 contiguous nucleotides of a polynucleotide of claim 12.

20

14. A method of detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 12, the method comprising:

25

a) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide or fragments thereof, and

b) detecting the presence or absence of said hybridization complex, and, optionally, if present, the amount thereof.

30

15. A method of claim 14, wherein the probe comprises at least 60 contiguous nucleotides.

16. A method of detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 12, the method comprising:

35

a) amplifying said target polynucleotide or fragment thereof using polymerase chain

- reaction amplification, and
- b) detecting the presence or absence of said amplified target polynucleotide or fragment thereof, and, optionally, if present, the amount thereof.

5 17. A composition comprising a polypeptide of claim 1 and a pharmaceutically acceptable excipient.

18. A composition of claim 17, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NO:1-20.

10

19. A method for treating a disease or condition associated with decreased expression of functional KAP, comprising administering to a patient in need of such treatment the composition of claim 17.

15 20. A method of screening a compound for effectiveness as an agonist of a polypeptide of claim 1, the method comprising:

- a) exposing a sample comprising a polypeptide of claim 1 to a compound, and
- b) detecting agonist activity in the sample.

20 21. A composition comprising an agonist compound identified by a method of claim 20 and a pharmaceutically acceptable excipient.

22. A method for treating a disease or condition associated with decreased expression of functional KAP, comprising administering to a patient in need of such treatment a  
25 composition of claim 21.

23. A method of screening a compound for effectiveness as an antagonist of a polypeptide of claim 1, the method comprising:

- a) exposing a sample comprising a polypeptide of claim 1 to a compound, and
- 30 b) detecting antagonist activity in the sample.

24. A composition comprising an antagonist compound identified by a method of claim 23 and a pharmaceutically acceptable excipient.

35 25. A method for treating a disease or condition associated with overexpression of

functional KAP, comprising administering to a patient in need of such treatment a composition of claim 24.

5 26. A method of screening for a compound that specifically binds to the polypeptide of claim 1, the method comprising:

- a) combining the polypeptide of claim 1 with at least one test compound under suitable conditions, and
- b) detecting binding of the polypeptide of claim 1 to the test compound, thereby identifying a compound that specifically binds to the polypeptide of claim 1.

10

27. A method of screening for a compound that modulates the activity of the polypeptide of claim 1, the method comprising:

- a) combining the polypeptide of claim 1 with at least one test compound under conditions permissive for the activity of the polypeptide of claim 1,
- 15 b) assessing the activity of the polypeptide of claim 1 in the presence of the test compound, and
- c) comparing the activity of the polypeptide of claim 1 in the presence of the test compound with the activity of the polypeptide of claim 1 in the absence of the test compound, wherein a change in the activity of the polypeptide of claim 1 in the presence of the test compound is indicative of a compound that modulates the activity of the polypeptide of claim 1.

20

28. A method of screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a sequence of claim 5, the method comprising:

25

- a) exposing a sample comprising the target polynucleotide to a compound, under conditions suitable for the expression of the target polynucleotide,
- b) detecting altered expression of the target polynucleotide, and
- c) comparing the expression of the target polynucleotide in the presence of varying amounts of the compound and in the absence of the compound.

30

29. A method of assessing toxicity of a test compound, the method comprising:

- a) treating a biological sample containing nucleic acids with the test compound,
- b) hybridizing the nucleic acids of the treated biological sample with a probe comprising at least 20 contiguous nucleotides of a polynucleotide of claim 12 under

35

conditions whereby a specific hybridization complex is formed between said probe and a target polynucleotide in the biological sample, said target polynucleotide comprising a polynucleotide sequence of a polynucleotide of claim 12 or fragment thereof,

- 5      c)      quantifying the amount of hybridization complex, and  
d)      comparing the amount of hybridization complex in the treated biological sample with the amount of hybridization complex in an untreated biological sample, wherein a difference in the amount of hybridization complex in the treated biological sample is indicative of toxicity of the test compound.

10

30. A diagnostic test for a condition or disease associated with the expression of KAP in a biological sample, the method comprising:

- 15      a)      combining the biological sample with an antibody of claim 11, under conditions suitable for the antibody to bind the polypeptide and form an antibody:polypeptide complex, and  
b)      detecting the complex, wherein the presence of the complex correlates with the presence of the polypeptide in the biological sample.

31. The antibody of claim 11, wherein the antibody is:

- 20      a)      a chimeric antibody,  
b)      a single chain antibody,  
c)      a Fab fragment,  
d)      a F(ab')<sub>2</sub> fragment, or  
e)      a humanized antibody.

25

32. A composition comprising an antibody of claim 11 and an acceptable excipient.

33. A method of diagnosing a condition or disease associated with the expression of KAP in a subject, comprising administering to said subject an effective amount of the composition of claim 32.

30

34. A composition of claim 32, wherein the antibody is labeled.

35. A method of diagnosing a condition or disease associated with the expression of KAP in a subject, comprising administering to said subject an effective amount of the

35

composition of claim 34.

36. A method of preparing a polyclonal antibody with the specificity of the antibody of claim 11, the method comprising:

- 5 a) immunizing an animal with a polypeptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NO:1-20, or an immunogenic fragment thereof, under conditions to elicit an antibody response,
- b) isolating antibodies from said animal, and
- 10 c) screening the isolated antibodies with the polypeptide, thereby identifying a polyclonal antibody which binds specifically to a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-20.

37. A polyclonal antibody produced by a method of claim 36.

15 38. A composition comprising the polyclonal antibody of claim 37 and a suitable carrier.

39. A method of making a monoclonal antibody with the specificity of the antibody of claim 11, the method comprising:

- 20 a) immunizing an animal with a polypeptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NO:1-20, or an immunogenic fragment thereof, under conditions to elicit an antibody response,
- b) isolating antibody producing cells from the animal,
- c) fusing the antibody producing cells with immortalized cells to form monoclonal antibody-producing hybridoma cells,
- 25 d) culturing the hybridoma cells, and
- e) isolating from the culture monoclonal antibody which binds specifically to a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-20.

30 40. A monoclonal antibody produced by a method of claim 39.

41. A composition comprising the monoclonal antibody of claim 40 and a suitable carrier.

42. The antibody of claim 11, wherein the antibody is produced by screening a Fab  
35 expression library.

43. The antibody of claim 11, wherein the antibody is produced by screening a recombinant immunoglobulin library.

44. A method of detecting a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-20 in a sample, the method comprising:

- a) incubating the antibody of claim 11 with a sample under conditions to allow specific binding of the antibody and the polypeptide, and
- b) detecting specific binding, wherein specific binding indicates the presence of a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-20 in the sample.

45. A method of purifying a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-20 from a sample, the method comprising:

- a) incubating the antibody of claim 11 with a sample under conditions to allow specific binding of the antibody and the polypeptide, and
- b) separating the antibody from the sample and obtaining the purified polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-20.

46. A microarray wherein at least one element of the microarray is a polynucleotide of claim 13.

47. A method of generating an expression profile of a sample which contains polynucleotides, the method comprising:

- a) labeling the polynucleotides of the sample,
- b) contacting the elements of the microarray of claim 46 with the labeled polynucleotides of the sample under conditions suitable for the formation of a hybridization complex, and
- c) quantifying the expression of the polynucleotides in the sample.

48. An array comprising different nucleotide molecules affixed in distinct physical locations on a solid substrate, wherein at least one of said nucleotide molecules comprises a first oligonucleotide or polynucleotide sequence specifically hybridizable with at least 30 contiguous nucleotides of a target polynucleotide, and wherein said target polynucleotide is a polynucleotide of claim 12.



49. An array of claim 48, wherein said first oligonucleotide or polynucleotide sequence is completely complementary to at least 30 contiguous nucleotides of said target polynucleotide.

5 50. An array of claim 48, wherein said first oligonucleotide or polynucleotide sequence is completely complementary to at least 60 contiguous nucleotides of said target polynucleotide.

10 51. An array of claim 48, wherein said first oligonucleotide or polynucleotide sequence is completely complementary to said target polynucleotide.

52. An array of claim 48, which is a microarray.

15 53. An array of claim 48, further comprising said target polynucleotide hybridized to a nucleotide molecule comprising said first oligonucleotide or polynucleotide sequence.

54. An array of claim 48, wherein a linker joins at least one of said nucleotide molecules to said solid substrate.

20 55. An array of claim 48, wherein each distinct physical location on the substrate contains multiple nucleotide molecules, and the multiple nucleotide molecules at any single distinct physical location have the same sequence, and each distinct physical location on the substrate contains nucleotide molecules having a sequence which differs from the sequence of nucleotide molecules at another distinct physical location on the substrate.

25 56. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:1.

57. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:2.

30 58. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:3.

59. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:4.

60. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:5.

35

61. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:6.
62. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:7.
- 5 63. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:8.
64. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:9.
65. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:10.
- 10 66. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:11.
67. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:12.
- 15 68. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:13.
69. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:14.
70. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:15.
- 20 71. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:16.
72. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:17.
- 25 73. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:18.
74. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:19.
75. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:20.
- 30
76. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:21.

77. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:22.

5 78. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:23.

79. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:24.

10 80. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:25.

81. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:26.

15 82. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:27.

83. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:28.

84. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:29.

25 85. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:30.

86. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:31.

30 87. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:32.

88. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:33.

35

89. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:34.

5 90. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:35.

91. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:36.

10 92. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:37.

93. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:38.

15 94. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:39.

20 95. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:40.

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&lt;110&gt; INCYTE GENOMICS, INC.

YUE, Henry  
 DING, Li  
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 BURFORD, Neil  
 BANDMAN, Olga  
 THORNTON, Michael  
 KHAN, Farrah A.  
 WALIA, Narinder K.  
 NGUYEN, Danniel B.  
 ELLIOTT, Vicki S.  
 XU, Yuming  
 LU, Yan  
 HAFALIA, April J.A.  
 YAO, Monique G.  
 GANDHI, Ameena R.  
 ARVIZU, Chandra  
 FORSYTHE, Ian

&lt;120&gt; KINASES AND PHOSPHATASES

&lt;130&gt; PI-0311 PCT

&lt;140&gt; To Be Assigned

&lt;141&gt; Herewith

<150> 60/254,034; 60/251,814; 60/255,756; 60/256,172; 60/257,416  
 60/260,912; 60/264,344; 60/266,017

<151> 2000-12-06; 2000-12-07; 2000-12-14; 2000-12-15; 2000-12-22;  
 2001-01-10; 2001-01-25; 2001-02-02

&lt;160&gt; 40

&lt;170&gt; PERL Program

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&lt;211&gt; 1636

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 4615110CD1

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Leu	Lys	Asn	Tyr	Gly	Glu	Asn	Pro	Glu	Ala	Tyr	Asn	Glu	Glu	Leu	45
				35					40						
Lys	Lys	Leu	Glu	Leu	Leu	Arg	Gln	Asn	Ala	Val	Arg	Val	Pro	Arg	60
				50					55						
Asp	Phe	Glu	Gly	Cys	Ser	Val	Leu	Arg	Lys	Tyr	Leu	Gly	Gln	Leu	75
				65					70						
His	Tyr	Leu	Gln	Ser	Arg	Val	Pro	Met	Gly	Ser	Gly	Gln	Glu	Ala	90
				80					85						

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Ala His Glu Asp Ile Lys Tyr Glu Gln Ala Cys Ile Leu Tyr Asn		
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Ser Glu Glu Gly Met Lys Val Ser Cys Thr His Phe Gln Cys Ala		
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Ala Gly Ala Phe Ala Tyr Leu Arg Glu His Phe Pro Gln Ala Tyr		
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Ser Val Asp Met Ser Arg Gln Ile Leu Thr Leu Asn Val Asn Leu		
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	185	190 195
Asp Asn Arg Lys Ser Phe Leu Val Ala Arg Ile Ser Ala Gln Val		
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Val Asp Tyr Tyr Lys Glu Ala Cys Arg Ala Leu Glu Asn Pro Asp		
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Thr Ala Ser Leu Leu Gly Arg Ile Gln Lys Asp Trp Lys Lys Leu		
	230	235 240
Val Gln Met Lys Ile Tyr Tyr Phe Ala Ala Val Ala His Leu His		
	245	250 255
Met Gly Lys Gln Ala Glu Glu Gln Gln Lys Phe Gly Glu Arg Val		
	260	265 270
Ala Tyr Phe Gln Ser Ala Leu Asp Lys Leu Asn Glu Ala Ile Lys		
	275	280 285
Leu Ala Lys Gly Gln Pro Asp Thr Val Gln Asp Ala Leu Arg Phe		
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Thr Met Asp Val Ile Gly Gly Lys Tyr Asn Ser Ala Lys Lys Asp		
	305	310 315
Asn Asp Phe Ile Tyr His Glu Ala Val Pro Ala Leu Asp Thr Leu		
	320	325 330
Gln Pro Val Lys Gly Ala Pro Leu Val Lys Pro Leu Pro Val Asn		
	335	340 345
Pro Thr Asp Pro Ala Val Thr Gly Pro Asp Ile Phe Ala Lys Leu		
	350	355 360
Val Pro Met Ala Ala His Glu Ala Ser Ser Leu Tyr Ser Glu Glu		
	365	370 375
Lys Ala Lys Leu Leu Arg Glu Met Met Ala Lys Ile Glu Asp Lys		
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Asn Glu Val Leu Asp Gln Phe Met Asp Ser Met Gln Leu Asp Pro		
	395	400 405
Glu Thr Val Asp Asn Leu Asp Ala Tyr Ser His Ile Pro Pro Gln		
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Leu Met Glu Lys Cys Ala Ala Leu Ser Val Arg Pro Asp Thr Val		
	425	430 435
Arg Asn Leu Val Gln Ser Met Gln Val Leu Ser Gly Val Phe Thr		
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Asp Val Glu Ala Ser Leu Lys Asp Ile Arg Asp Leu Leu Glu Glu		
	455	460 465
Asp Glu Leu Leu Glu Gln Lys Phe Gln Glu Ala Val Gly Gln Ala		
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Gly Ala Ile Ser Ile Thr Ser Lys Ala Glu Leu Ala Glu Val Arg		
	485	490 495
Arg Glu Trp Ala Lys Tyr Met Glu Val His Glu Lys Ala Ser Phe		
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Thr Asn Ser Glu Leu His Arg Ala Met Asn Leu His Val Gly Asn		
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Pro Thr Pro Ala Leu Ser Pro Glu Asp Lys Ala Val Leu Gln Asn		
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Leu Lys Arg Ile Leu Ala Lys Val Gln Glu Met Arg Asp Gln Arg		

Val Ser Leu Glu	Gln Gln Leu Arg Glu	Leu Ile Gln Lys Asp	Asp	560	565	570
Ile Thr Ala Ser	Leu Val Thr Thr Asp	His Ser Glu Met Lys	Lys	575	580	585
Leu Phe Glu Glu	Gln Leu Lys Lys Tyr	Asp Gln Leu Lys Val	Tyr	590	595	600
Leu Glu Gln Asn	Leu Ala Ala Gln Asp	Arg Val Leu Cys Ala	Leu	605	610	615
Thr Glu Ala Asn	Val Gln Tyr Ala Ala	Val Arg Arg Val Leu	Ser	620	625	630
Asp Leu Asp Gln	Lys Trp Asn Ser Thr	Leu Gln Thr Leu Val	Ala	635	640	645
Ser Tyr Glu Ala	Tyr Glu Asp Leu Met	Lys Lys Ser Gln Glu	Gly	650	655	660
Arg Asp Phe Tyr	Ala Asp Leu Glu Ser	Lys Val Ala Ala Leu	Leu	665	670	675
Glu Arg Thr Gln	Ser Thr Cys Gln Ala	Arg Glu Ala Ala Arg	Gln	680	685	690
Gln Leu Leu Asp	Arg Glu Leu Lys Lys	Lys Pro Pro Pro Arg	Pro	695	700	705
Thr Ala Pro Lys	Pro Leu Leu Pro Arg	Arg Glu Glu Ser Glu	Ala	710	715	720
Val Glu Ala Gly	Asp Pro Pro Glu Glu	Leu Arg Ser Leu Pro	Pro	725	730	735
Asp Met Val Ala	Gly Pro Arg Leu Pro	Asp Thr Phe Leu Gly	Ser	740	745	750
Ala Thr Pro Leu	His Phe Pro Pro Ser	Pro Phe Pro Ser Ser	Thr	755	760	765
Gly Pro Gly Pro	His Tyr Leu Ser Gly	Pro Leu Pro Pro Gly	Thr	770	775	780
Tyr Ser Gly Pro	Thr Gln Leu Ile Gln	Pro Arg Ala Pro Gly	Pro	785	790	795
His Ala Met Pro	Val Ala Pro Gly Pro	Ala Leu Tyr Pro Ala	Pro	800	805	810
Ala Tyr Thr Pro	Glu Leu Gly Leu Val	Pro Arg Ser Ser Pro	Gln	815	820	825
His Gly Val Val	Ser Ser Pro Tyr Val	Gly Val Gly Pro Ala	Pro	830	835	840
Pro Val Ala Gly	Leu Pro Ser Ala Pro	Pro Pro Gln Phe Ser	Gly	845	850	855
Pro Glu Leu Ala	Met Ala Val Arg Pro	Ala Thr Thr Thr Val	Asp	860	865	870
Ser Ile Gln Ala	Pro Ile Pro Ser His	Thr Ala Pro Arg Pro	Asn	875	880	885
Pro Thr Pro Ala	Pro Pro Pro Pro Cys	Phe Pro Val Pro Pro	Pro	890	895	900
Gln Pro Leu Pro	Thr Pro Tyr Thr Tyr	Pro Ala Gly Ala Lys	Gln	905	910	915
Pro Ile Pro Ala	Gln His His Phe Ser	Ser Gly Ile Pro Thr	Gly	920	925	930
Phe Pro Ala Pro	Arg Ile Gly Pro Gln	Pro Gln Pro His Pro	Gln	935	940	945
Pro His Pro Ser	Gln Ala Phe Gly Pro	Gln Pro Pro Gln Gln	Pro	950	955	960
Leu Pro Leu Gln	His Pro His Leu Phe	Pro Pro Gln Ala Pro	Gly	965	970	975
Leu Leu Pro Pro	Gln Ser Pro Tyr Pro	Tyr Ala Pro Gln Pro	Gly	980	985	990
Val Leu Gly Gln	Pro Pro Pro Pro Leu	His Thr Gln Leu Tyr	Pro	995	1000	1005
Gly Pro Ala Gln	Asp Pro Leu Pro Ala	His Ser Gly Ala Leu	Pro	1010	1015	1020
				1025	1030	1035

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 1040 1045  
 Tyr Gly Pro Ala Pro Ser Thr Arg Pro Met Gly Pro Gln Ala Ala 1065  
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 Pro Leu Thr Ile Arg Gly Pro Ser Ser Ala Gly Gln Ser Thr Pro 1080  
 1070 1075  
 Ser Pro His Leu Val Pro Ser Pro Ala Pro Ser Pro Gly Pro Gly 1095  
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 Pro Val Pro Pro Arg Pro Pro Ala Ala Glu Pro Pro Pro Cys Leu 1110  
 1100 1105  
 Arg Arg Gly Ala Ala Ala Ala Asp Leu Leu Ser Ser Ser Pro Glu 1125  
 1115 1120  
 Ser Gln His Gly Gly Thr Gln Ser Pro Gly Gly Gly Gln Pro Leu 1140  
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 Glu Arg Gly Gln Pro Met Val His Gly Ala Leu Ser Leu Ala Leu 1320  
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 Leu Gln Phe Arg Asp Gln Ser Leu Lys Arg Ser Leu Val His Leu 1350  
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 His Leu Arg Phe Cys Tyr Glu Ala Val Val Arg His Val Glu Gln 1455  
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 Val Leu Gln Arg His Gly Val Pro Pro Pro Cys Lys Pro Leu Ala 1470  
 1460 1465  
 Ser Ala Ser Ile Ser Gln Lys Asn His Leu Pro Gln Asp Ser Gln 1485  
 1475 1480  
 Asp Leu Val Leu Gly Gly Asp Val Pro Ile Ser Ser Ile Gln Ala 1500  
 1490 1495  
 Thr Ile Ala Lys Leu Ser Ile Arg Pro Pro Gly Gly Leu Glu Ser



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Pro Val Ala Ser Leu	Pro Gly Pro Ala Glu	Pro Pro Gly Leu Pro
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Pro Ala Ser Leu Pro	Glu Ser Thr Pro Ile	Pro Ser Ser Ser Pro
1535	1540	1545
Pro Pro Leu Ser Ser	Pro Leu Pro Glu Ala	Pro Gln Pro Lys Glu
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Glu Pro Pro Val Pro	Glu Ala Pro Ser Ser	Gly Pro Pro Ser Ser
1565	1570	1575
Ser Leu Glu Leu Leu	Ala Ser Leu Thr Pro	Glu Ala Phe Ser Leu
1580	1585	1590
Asp Ser Ser Leu Arg	Gly Lys Gln Arg Met	Ser Lys His Asn Phe
1595	1600	1605
Leu Gln Ala His Asn	Gly Gln Gly Leu Arg	Ala Thr Arg Pro Ser
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Asp Asp Pro Leu Ser	Leu Leu Asp Pro Leu	Trp Thr Leu Asn Lys
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Thr

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&lt;211&gt; 673

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 4622229CD1

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	35	40
Thr Leu Asp Ser Pro	Thr Gly Ser His Val	Glu Trp Cys Lys Gln
	50	55
Leu Ile Ala Ala Thr	Ile Ser Ser Gln Ile	Ser Gly Ser Val Thr
	65	70
Ser Glu Asn Val Ser	Arg Asp Tyr Lys Val	Phe Arg Arg Pro Asp
	80	85
Leu Arg Ala Leu Arg	Asp Gly Asn Lys Leu	Ala Gln Met Glu Glu
	95	100
Ala Pro Leu Phe Pro	Gly Glu Ser Ile Lys	Ala Ile Val Lys Asp
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Val Met Tyr Ile Cys	Pro Phe Met Gly Ala	Val Ser Gly Thr Leu
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Thr Val Thr Asp Phe	Lys Leu Tyr Phe Lys	Asn Val Glu Arg Asp
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Pro His Phe Ile Leu	Asp Val Pro Leu Gly	Val Ile Ser Arg Val
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Glu Lys Ile Gly Ala	Gln Ser His Gly Asp	Asn Ser Cys Gly Ile
	170	175
Glu Ile Val Cys Lys	Asp Met Arg Asn Leu	Arg Leu Ala Tyr Lys
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Gln Glu Glu Gln Ser	Lys Leu Gly Ile Phe	Glu Asn Leu Asn Lys
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His Ala Phe Pro Leu	Ser Asn Gly Gln Ala	Leu Phe Ala Phe Ser
	215	220
Tyr Lys Glu Lys Phe	Pro Ile Asn Gly Trp	Lys Val Tyr Asp Pro
	230	235
Val Ser Glu Tyr Lys	Arg Gln Gly Leu Pro	Asn Glu Ser Trp Lys

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Lys Val Ala Ala	290	Phe Arg Ala Lys Gly	295	Arg Val Pro Val Leu	300
Trp Ile His Pro	305	Glu Ser Gln Ala Thr	310	Ile Thr Arg Cys Ser	315
Pro Leu Val Gly	320	Pro Asn Asp Lys Arg	325	Cys Lys Glu Asp Glu	330
Tyr Leu Gln Thr	335	Ile Met Asp Ala Asn	340	Ala Gln Ser His Lys	345
Ile Ile Phe Asp	350	Ala Arg Gln Asn Ser	355	Val Ala Asp Thr Asn	360
Thr Lys Gly Gly	365	Gly Tyr Glu Ser Glu	370	Ser Ala Tyr Pro Asn	375
Glu Leu Val Phe	380	Leu Glu Ile His Asn	385	Ile His Val Met Arg	390
Ser Leu Arg Lys	395	Leu Lys Glu Ile Val	400	Tyr Pro Ser Ile Asp	405
Ala Arg Trp Leu	410	Ser Asn Val Asp Gly	415	Thr His Trp Leu Glu	420
Ile Arg Met Leu	425	Leu Ala Gly Ala Val	430	Arg Ile Ala Asp Lys	435
Glu Ser Gly Lys	440	Thr Ser Val Val Val	445	His Cys Ser Asp Gly	450
Asp Arg Thr Ala	455	Gln Leu Thr Ser Leu	460	Ala Met Leu Met Leu	465
Ser Tyr Tyr Arg	470	Thr Ile Lys Gly Phe	475	Glu Thr Leu Val Glu	480
Glu Trp Ile Ser	485	Phe Gly His Arg Phe	490	Ala Leu Arg Val Gly	495
Gly Asn Asp Asn	500	His Ala Asp Ala Asp	505	Arg Ser Pro Ile Phe	510
Gln Phe Val Asp	515	Cys Val Trp Gln Met	520	Thr Arg Gln Phe Pro	525
Ala Phe Glu Phe	530	Asn Glu Leu Phe Leu	535	Ile Thr Ile Leu Asp	540
Leu Tyr Ser Cys	545	Leu Phe Gly Thr Phe	550	Leu Cys Asn Cys Glu	555
Gln Arg Phe Lys	560	Glu Asp Val Tyr Thr	565	Lys Thr Ile Ser Leu	570
Ser Tyr Ile Asn	575	Ser Gln Leu Asp Glu	580	Phe Ser Asn Pro Phe	585
Val Asn Tyr Glu	590	Asn His Val Leu Tyr	595	Pro Val Ala Ser Leu	600
His Leu Glu Leu	605	Trp Val Asn Tyr Tyr	610	Val Arg Trp Asn Pro	615
Met Arg Pro Gln	620	Met Pro Ile His Gln	625	Asn Leu Lys Glu Leu	630
Ala Val Arg Ala	635	Glu Leu Gln Lys Arg	640	Val Glu Gly Leu Gln	645
Glu Val Ala Thr	650	Arg Ala Val Ser Ser	655	Ser Ser Glu Arg Gly	660
Ser Pro Ser His	665	Ser Ala Thr Ser Val	670	His Thr Ser Val	

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&lt;211&gt; 459

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&lt;213&gt; Homo sapiens

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&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 72358203CD1

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Tyr	Arg	Arg	Pro	Arg	Phe	Leu	Arg	Gly	Ser	Ser	Ser	Ser	Pro	Gly	35	40	45	
Ala	Ala	Asp	Ala	Ser	Arg	Arg	Pro	Asp	Ser	Arg	Pro	Val	Arg	Ser	50	55	60	
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Trp	Ala	Leu	Phe	Asp	Gly	His	Gly	Gly	Pro	Ala	Ala	Ala	Ile	Leu	125	130	135	
Ala	Ala	Asn	Thr	Leu	His	Ser	Cys	Leu	Arg	Arg	Gln	Leu	Glu	Ala	140	145	150	
Val	Val	Glu	Gly	Leu	Val	Ala	Thr	Gln	Pro	Met	His	Leu	Asn		155	160	165	
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Gly	Lys	Leu	Tyr	Met	Ala	Asn	Ala	Gly	Asp	Ser	Arg	Ala	Ile	Leu	230	235	240	
Val	Arg	Arg	Asp	Glu	Ile	Arg	Pro	Leu	Ser	Phe	Glu	Phe	Thr	Pro	245	250	255	
Glu	Thr	Glu	Arg	Gln	Arg	Ile	Gln	Gln	Leu	Ala	Phe	Val	Tyr	Pro	260	265	270	
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His	Met	Ser	Gly	Trp	Ser	Tyr	Lys	Arg	Val	Glu	Lys	Ser	Asp	Leu	305	310	315	
Lys	Tyr	Pro	Leu	Ile	His	Gly	Gln	Gly	Arg	Gln	Ala	Arg	Leu	Leu	320	325	330	
Gly	Thr	Leu	Ala	Val	Ser	Arg	Gly	Leu	Gly	Asp	His	Gln	Leu	Arg	335	340	345	
Val	Leu	Asp	Thr	Asn	Ile	Gln	Leu	Lys	Pro	Phe	Leu	Leu	Ser	Val	350	355	360	
Pro	Gln	Val	Thr	Val	Leu	Asp	Val	Asp	Gln	Leu	Glu	Leu	Gln	Glu	365	370	375	
Asp	Asp	Val	Val	Val	Met	Ala	Thr	Asp	Gly	Leu	Trp	Asp	Val	Leu	380	385	390	
Ser	Asn	Glu	Gln	Val	Ala	Trp	Leu	Val	Arg	Ser	Phe	Leu	Pro	Gly	395	400	405	
Asn	Gln	Glu	Asp	Pro	His	Arg	Phe	Ser	Lys	Leu	Ala	Gln	Met	Leu	410	415	420	
Ile	His	Ser	Thr	Gln	Gly	Lys	Glu	Asp	Ser	Leu	Thr	Glu	Glu	Gly	425	430	435	

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 Tyr Phe Arg His Leu Trp Asn Lys Ala Leu Leu Arg Ala Cys Ala  
 35 40 45  
 Asp Gly Gly Ala Asn Arg Leu Tyr Asp Ile Thr Glu Gly Glu Arg  
 50 55 60  
 Glu Ser Phe Leu Pro Glu Phe Ile Asn Gly Asp Phe Asp Ser Ile  
 65 70 75  
 Arg Pro Glu Val Arg Glu Tyr Tyr Ala Thr Lys Gly Cys Glu Leu  
 80 85 90  
 Ile Ser Thr Pro Asp Gln Asp His Thr Asp Phe Thr Lys Cys Leu  
 95 100 105  
 Lys Met Leu Gln Lys Lys Ile Glu Glu Lys Asp Leu Lys Val Asp  
 110 115 120  
 Val Ile Val Thr Leu Gly Gly Leu Ala Gly Arg Phe Asp Gln Ile  
 125 130 135  
 Met Ala Ser Val Asn Thr Leu Phe Gln Ala Thr His Ile Thr Pro  
 140 145 150  
 Phe Pro Ile Ile Ile Ile Gln Glu Glu Ser Leu Ile Tyr Leu Leu  
 155 160 165  
 Gln Pro Gly Lys His Arg Leu His Val Asp Thr Gly Met Glu Gly  
 170 175 180  
 Asp Trp Cys Gly Leu Ile Pro Val Gly Gln Pro Cys Met Gln Val  
 185 190 195  
 Thr Thr Thr Gly Leu Lys Trp Asn Leu Thr Asn Asp Val Leu Ala  
 200 205 210  
 Phe Gly Thr Leu Val Ser Thr Ser Asn Thr Tyr Asp Gly Ser Gly  
 215 220 225  
 Val Val Thr Val Glu Thr Asp His Pro Leu Leu Trp Thr Met Ala  
 230 235 240  
 Ile Lys Ser

<210> 5  
 <211> 632  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> Incyte ID No: 7484507CD1

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 Met Leu Gly Pro Gly Ser Asn Arg Arg Arg Pro Thr Gln Gly Glu  
 1 5 10 15  
 Arg Gly Pro Gly Ser Pro Gly Glu Pro Met Glu Lys Tyr Gln Val

				20					25					30
Leu	Tyr	Gln	Leu	Asn	Pro	Gly	Ala	Leu	Gly	Val	Asn	Leu	Val	Val
				35					40					45
Glu	Glu	Met	Glu	Thr	Lys	Val	Lys	His	Val	Ile	Lys	Gln	Val	Glu
				50					55					60
Cys	Met	Asp	Asp	His	Tyr	Ala	Ser	Gln	Ala	Leu	Glu	Glu	Leu	Met
				65					70					75
Pro	Leu	Leu	Lys	Leu	Arg	His	Ala	His	Ile	Ser	Val	Tyr	Gln	Glu
				80					85					90
Leu	Phe	Ile	Thr	Trp	Asn	Gly	Glu	Ile	Ser	Ser	Leu	Tyr	Leu	Cys
				95					100					105
Leu	Val	Met	Glu	Phe	Asn	Glu	Leu	Ser	Phe	Gln	Glu	Val	Ile	Glu
				110					115					120
Asp	Lys	Arg	Lys	Ala	Lys	Lys	Ile	Ile	Asp	Ser	Glu	Trp	Met	Gln
				125					130					135
Asn	Val	Leu	Gly	Gln	Val	Leu	Asp	Ala	Leu	Glu	Tyr	Leu	His	His
				140					145					150
Leu	Asp	Ile	Ile	His	Arg	Asn	Leu	Lys	Pro	Ser	Asn	Ile	Ile	Leu
				155					160					165
Ile	Ser	Ser	Asp	His	Cys	Lys	Leu	Gln	Asp	Leu	Ser	Ser	Asn	Val
				170					175					180
Leu	Met	Thr	Asp	Lys	Ala	Lys	Trp	Asn	Ile	Arg	Ala	Glu	Glu	Asp
				185					190					195
Pro	Phe	Arg	Lys	Ser	Trp	Met	Ala	Pro	Glu	Ala	Leu	Asn	Phe	Ser
				200					205					210
Phe	Ser	Gln	Lys	Ser	Asp	Ile	Trp	Ser	Leu	Gly	Cys	Ile	Ile	Leu
				215					220					225
Asp	Met	Thr	Ser	Cys	Ser	Phe	Met	Asp	Gly	Thr	Glu	Ala	Met	His
				230					235					240
Leu	Arg	Lys	Ser	Leu	Arg	Gln	Ser	Pro	Gly	Ser	Leu	Lys	Ala	Val
				245					250					255
Leu	Lys	Thr	Met	Glu	Glu	Lys	Gln	Ile	Pro	Asp	Val	Glu	Thr	Phe
				260					265					270
Arg	Asn	Leu	Leu	Pro	Leu	Met	Leu	Gln	Ile	Asp	Pro	Ser	Asp	Arg
				275					280					285
Ile	Thr	Ile	Lys	Asp	Val	Val	His	Ile	Thr	Phe	Leu	Arg	Gly	Ser
				290					295					300
Phe	Lys	Ser	Ser	Cys	Val	Ser	Leu	Thr	Leu	His	Arg	Gln	Met	Val
				305					310					315
Pro	Ala	Ser	Ile	Thr	Asp	Met	Leu	Leu	Glu	Gly	Asn	Val	Ala	Ser
				320					325					330
Ile	Leu	Gly	Asp	Ala	Gly	Asp	Thr	Lys	Gly	Glu	Arg	Ala	Leu	Lys
				335					340					345
Leu	Leu	Ser	Met	Ala	Leu	Ala	Ser	Tyr	Cys	Leu	Val	Pro	Glu	Gly
				350					355					360
Ser	Leu	Phe	Met	Pro	Leu	Ala	Leu	Leu	His	Met	His	Asp	Gln	Trp
				365					370					375
Leu	Ser	Cys	Asp	Gln	Asp	Arg	Val	Pro	Gly	Lys	Arg	Asp	Phe	Ala
				380					385					390
Ser	Leu	Gly	Lys	Leu	Gly	Lys	Leu	Leu	Gly	Pro	Ile	Pro	Lys	Gly
				395					400					405
Leu	Pro	Trp	Pro	Pro	Glu	Leu	Val	Glu	Val	Val	Val	Thr	Thr	Met
				410					415					420
Glu	Leu	His	Asp	Arg	Val	Leu	Asp	Val	Gln	Leu	Cys	Ala	Cys	Ser
				425					430					435
Leu	Leu	Leu	His	Leu	Leu	Gly	Gln	Gly	Ile	Ile	Val	Asn	Lys	Ala
				440					445					450
Pro	Leu	Glu	Lys	Val	Pro	Asp	Leu	Ile	Ser	Gln	Val	Leu	Ala	Thr
				455					460					465
Tyr	Pro	Ala	Asp	Gly	Glu	Met	Ala	Glu	Ala	Ser	Cys	Gly	Val	Phe
				470					475					480
Trp	Leu	Leu	Ser	Leu	Leu	Gly	Cys	Ile	Lys	Glu	Gln	Gln	Phe	Glu
				485					490					495

Gln	Val	Val	Ala	Leu	Leu	Leu	Gln	Ser	Ile	Arg	Leu	Cys	Gln	Asp
				500					505					510
Arg	Ala	Leu	Leu	Val	Asn	Asn	Ala	Tyr	Arg	Gly	Leu	Ala	Ser	Leu
				515					520					525
Val	Lys	Val	Ser	Glu	Leu	Ala	Ala	Phe	Lys	Val	Val	Val	Gln	Glu
				530					535					540
Glu	Gly	Gly	Ser	Gly	Leu	Ser	Leu	Ile	Lys	Glu	Thr	Tyr	Gln	Leu
				545					550					555
His	Arg	Asp	Asp	Pro	Glu	Val	Val	Glu	Asn	Val	Gly	Met	Leu	Leu
				560					565					570
Val	His	Leu	Ala	Ser	Tyr	Glu	Glu	Ile	Leu	Pro	Glu	Leu	Val	Ser
				575					580					585
Ser	Ser	Met	Lys	Ala	Leu	Leu	Gln	Glu	Ile	Lys	Glu	Arg	Phe	Thr
				590					595					600
Ser	Ser	Leu	Glu	Leu	Val	Ser	Cys	Ala	Glu	Lys	Val	Leu	Leu	Arg
				605					610					615
Leu	Glu	Ala	Ala	Thr	Ser	Pro	Ser	Pro	Leu	Gly	Gly	Glu	Ala	Ala
				620					625					630
Gln	Pro													

&lt;210&gt; 6

&lt;211&gt; 1511

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 7198931CD1

&lt;400&gt; 6

Met	Ala	Ala	Ala	Ala	Gly	Asn	Arg	Ala	Ser	Ser	Ser	Gly	Phe	Pro
1				5					10					15
Gly	Ala	Arg	Ala	Thr	Ser	Pro	Glu	Ala	Gly	Gly	Gly	Gly	Gly	Ala
				20					25					30
Leu	Lys	Ala	Ser	Ser	Ala	Arg	Ala	Ala	Ala	Ala	Gly	Leu	Leu	Arg
				35					40					45
Glu	Ala	Gly	Ser	Gly	Gly	Arg	Glu	Arg	Ala	Asp	Trp	Arg	Arg	Arg
				50					55					60
Gln	Leu	Arg	Lys	Val	Arg	Ser	Val	Glu	Leu	Asp	Gln	Leu	Pro	Glu
				65					70					75
Gln	Pro	Leu	Phe	Leu	Ala	Ala	Ser	Pro	Pro	Ala	Ser	Ser	Thr	Ser
				80					85					90
Pro	Ser	Pro	Glu	Pro	Ala	Asp	Ala	Ala	Gly	Ser	Gly	Thr	Gly	Phe
				95					100					105
Gln	Pro	Val	Ala	Val	Pro	Pro	Pro	His	Gly	Ala	Ala	Ser	Arg	Arg
				110					115					120
Gly	Ala	His	Leu	Thr	Glu	Ser	Val	Ala	Ala	Pro	Asp	Ser	Gly	Ala
				125					130					135
Ser	Ser	Pro	Ala	Ala	Ala	Glu	Pro	Gly	Glu	Lys	Arg	Ala	Pro	Ala
				140					145					150
Ala	Glu	Pro	Ser	Pro	Ala	Ala	Ala	Pro	Ala	Gly	Arg	Glu	Met	Glu
				155					160					165
Asn	Lys	Glu	Thr	Leu	Lys	Gly	Leu	His	Lys	Met	Asp	Asp	Arg	Pro
				170					175					180
Glu	Glu	Arg	Met	Ile	Arg	Glu	Lys	Leu	Lys	Ala	Thr	Cys	Met	Pro
				185					190					195
Ala	Trp	Lys	His	Glu	Trp	Leu	Glu	Arg	Arg	Asn	Arg	Arg	Gly	Pro
				200					205					210
Val	Val	Val	Lys	Pro	Ile	Pro	Val	Lys	Gly	Asp	Gly	Ser	Glu	Met
				215					220					225
Asn	His	Leu	Ala	Ala	Glu	Ser	Pro	Gly	Glu	Val	Gln	Ala	Ser	Ala
				230					235					240

Ala	Ser	Pro	Ala	Ser	Lys	Gly	Arg	Arg	Ser	Pro	Ser	Pro	Gly	Asn
				245					250					255
Ser	Pro	Ser	Gly	Arg	Thr	Val	Lys	Ser	Glu	Ser	Pro	Gly	Val	Arg
				260					265					270
Arg	Lys	Arg	Val	Ser	Pro	Val	Pro	Phe	Gln	Ser	Gly	Arg	Ile	Thr
				275					280					285
Pro	Pro	Arg	Arg	Ala	Pro	Ser	Pro	Asp	Gly	Phe	Ser	Pro	Tyr	Ser
				290					295					300
Pro	Glu	Glu	Thr	Asn	Arg	Arg	Val	Asn	Lys	Val	Met	Arg	Ala	Arg
				305					310					315
Leu	Tyr	Leu	Leu	Gln	Gln	Ile	Gly	Pro	Asn	Ser	Phe	Leu	Ile	Gly
				320					325					330
Gly	Asp	Ser	Pro	Asp	Asn	Lys	Tyr	Arg	Val	Phe	Ile	Gly	Pro	Gln
				335					340					345
Asn	Cys	Ser	Cys	Ala	Arg	Gly	Thr	Phe	Cys	Ile	His	Leu	Leu	Phe
				350					355					360
Val	Met	Leu	Arg	Val	Phe	Gln	Leu	Glu	Pro	Ser	Asp	Pro	Met	Leu
				365					370					375
Trp	Arg	Lys	Thr	Leu	Lys	Asn	Phe	Glu	Val	Glu	Ser	Leu	Phe	Gln
				380					385					390
Lys	Tyr	His	Ser	Arg	Arg	Ser	Ser	Arg	Ile	Lys	Ala	Pro	Ser	Arg
				395					400					405
Asn	Thr	Ile	Gln	Lys	Phe	Val	Ser	Arg	Met	Ser	Asn	Ser	His	Thr
				410					415					420
Leu	Ser	Ser	Ser	Ser	Thr	Ser	Thr	Ser	Ser	Ser	Glu	Asn	Ser	Ile
				425					430					435
Lys	Asp	Glu	Glu	Glu	Gln	Met	Cys	Pro	Ile	Cys	Leu	Leu	Gly	Met
				440					445					450
Leu	Asp	Glu	Glu	Ser	Leu	Thr	Val	Cys	Glu	Asp	Gly	Cys	Arg	Asn
				455					460					465
Lys	Leu	His	His	His	Cys	Met	Ser	Ile	Trp	Ala	Glu	Glu	Cys	Arg
				470					475					480
Arg	Asn	Arg	Glu	Pro	Leu	Ile	Cys	Pro	Leu	Cys	Arg	Ser	Lys	Trp
				485					490					495
Arg	Ser	His	Asp	Phe	Tyr	Ser	His	Glu	Leu	Ser	Ser	Pro	Val	Asp
				500					505					510
Ser	Pro	Ser	Ser	Leu	Arg	Ala	Ala	Gln	Gln	Gln	Thr	Val	Gln	Gln
				515					520					525
Gln	Pro	Leu	Ala	Gly	Ser	Arg	Arg	Asn	Gln	Glu	Ser	Asn	Phe	Asn
				530					535					540
Leu	Thr	His	Tyr	Gly	Thr	Gln	Gln	Ile	Pro	Pro	Ala	Tyr	Lys	Asp
				545					550					555
Leu	Ala	Glu	Pro	Trp	Ile	Gln	Val	Phe	Gly	Met	Glu	Leu	Val	Gly
				560					565					570
Cys	Leu	Phe	Ser	Arg	Asn	Trp	Asn	Val	Arg	Glu	Met	Ala	Leu	Arg
				575					580					585
Arg	Leu	Ser	His	Asp	Val	Ser	Gly	Ala	Leu	Leu	Leu	Ala	Asn	Gly
				590					595					600
Glu	Ser	Thr	Gly	Asn	Ser	Gly	Gly	Ser	Ser	Gly	Ser	Ser	Pro	Ser
				605					610					615
Gly	Gly	Ala	Thr	Ser	Gly	Ser	Ser	Gln	Thr	Ser	Ile	Ser	Gly	Asp
				620					625					630
Val	Val	Glu	Ala	Cys	Cys	Ser	Val	Leu	Ser	Met	Val	Cys	Ala	Asp
				635					640					645
Pro	Val	Tyr	Lys	Val	Tyr	Val	Ala	Ala	Leu	Lys	Thr	Leu	Arg	Ala
				650					655					660
Met	Leu	Val	Tyr	Thr	Pro	Cys	His	Ser	Leu	Ala	Glu	Arg	Ile	Lys
				665					670					675
Leu	Gln	Arg	Leu	Leu	Gln	Pro	Val	Val	Asp	Thr	Ile	Leu	Val	Lys
				680					685					690
Cys	Ala	Asp	Ala	Asn	Ser	Arg	Thr	Ser	Gln	Leu	Ser	Ile	Ser	Thr
				695					700					705
Leu	Leu	Glu	Leu	Cys	Lys	Gly	Gln	Ala	Gly	Glu	Leu	Ala	Val	Gly

Arg Glu Ile Leu	710	Ala Gly Ser Ile	715	Ile Gly Gly Val	720
	725		730		735
Tyr Val Leu Asn	740	Cys Ile Leu Gly Asn	745	Gln Thr Glu Ser Asn	750
	755		760		765
Trp Gln Glu Leu	770	Leu Gly Arg Leu Cys	775	Leu Ile Asp Arg Leu	780
	785		790		795
Leu Glu Phe Pro	800	Ala Glu Phe Tyr Pro	805	His Ile Val Ser Thr	810
	815		820		825
Val Ser Gln Ala	830	Glu Pro Val Glu Ile	835	Arg Tyr Lys Lys Leu	840
	845		850		855
Ser Leu Leu Thr	860	Phe Ala Leu Gln Ser	865	Ile Asn Asn Ser His	870
	875		880		885
Met Val Gly Lys	890	Leu Ser Arg Arg Ile	895	Tyr Leu Ser Ser Ala	900
	905		910		915
Met Val Thr Thr	920	Val Pro His Val Phe	925	Ser Lys Leu Leu Glu	930
	935		940		945
Leu Ser Val Ser	950	Ser Ser Thr His Phe	955	Thr Arg Met Arg Arg	960
	965		970		975
Leu Met Ala Ile	980	Thr Asp Glu Val Glu	985	Ile Ala Glu Ala Ile	990
	995		1000		1005
Leu Gly Val Glu	1010	Asp Thr Leu Asp Gly	1015	Gln Gln Asp Ser Phe	1020
	1025		1030		1035
Gln Ala Ser Val	1040	Pro Asn Asn Tyr Leu	1045	Glu Thr Thr Glu Asn	1050
	1055		1060		1065
Ser Pro Glu Cys	1070	Thr Ile His Leu Glu	1075	Lys Thr Gly Lys Gly	1080
	1085		1090		1095
Cys Ala Thr Lys	1100	Leu Ser Ala Ser Ser	1105	Glu Asp Ile Ser Glu	1110
	1115		1120		1125
Leu Ala Ser Ile	1130	Ser Val Gly Pro Ser	1135	Ser Ser Thr Thr Thr	1140
	1145		1150		1155
Thr Thr Thr Glu	1160	Gln Pro Lys Pro Met	1165	Val Gln Thr Lys Gly	1170
	1175		1180		1185
Pro His Ser Gln		Cys Leu Asn Ser Ser		Pro Leu Ser His His	
Gln Leu Met Phe		Pro Ala Leu Ser Thr		Pro Ser Ser Ser Thr	
Ser Val Pro Ala		Gly Thr Ala Thr Asp		Val Ser Lys His Arg	
Gln Gly Phe Ile		Pro Cys Arg Ile Pro		Ser Ala Ser Pro Gln	
Gln Arg Lys Phe		Ser Leu Gln Phe His		Arg Asn Cys Pro Glu	
Lys Asp Ser Asp		Lys Leu Ser Pro Val		Phe Thr Gln Ser Arg	
Leu Pro Ser Ser		Asn Ile His Arg Pro		Lys Pro Ser Arg Pro	
Pro Gly Asn Thr		Ser Lys Gln Gly Asp		Pro Ser Lys Asn Ser	
Thr Leu Asp Leu		Asn Ser Ser Ser Lys		Cys Asp Asp Ser Phe	
Cys Ser Ser Asn		Ser Ser Asn Ala Val		Ile Pro Ser Asp Glu	
Val Phe Thr Pro		Val Glu Glu Lys Cys		Arg Leu Asp Val Asn	
Glu Leu Asn Ser		Ser Ile Glu Asp Leu		Glu Ala Ser Met Pro	
Ser Ser Asp Thr		Thr Val Thr Phe Lys		Ser Glu Val Ala Val	
Ser Pro Glu Lys		Ala Glu Asn Asp Asp		Thr Tyr Lys Asp Asp	
Asn His Asn Gln		Lys Cys Lys Glu Lys		Met Glu Ala Glu Glu	



Glu Ala Leu Ala Ile Ala Met Ala Met Ser Ala Ser Gln Asp Ala  
 1190 1195 1200  
 Leu Pro Ile Val Pro Gln Leu Gln Val Glu Asn Gly Glu Asp Ile  
 1205 1210 1215  
 Ile Ile Ile Gln Gln Asp Thr Pro Glu Thr Leu Pro Gly His Thr  
 1220 1225 1230  
 Lys Ala Lys Gln Pro Tyr Arg Glu Asp Thr Glu Trp Leu Lys Gly  
 1235 1240 1245  
 Gln Gln Ile Gly Leu Gly Ala Phe Ser Ser Cys Tyr Gln Ala Gln  
 1250 1255 1260  
 Asp Val Gly Thr Gly Thr Leu Met Ala Val Lys Gln Val Thr Tyr  
 1265 1270 1275  
 Val Arg Asn Thr Ser Ser Glu Gln Glu Glu Val Val Glu Ala Leu  
 1280 1285 1290  
 Arg Glu Glu Ile Arg Met Met Ser His Leu Asn His Pro Asn Ile  
 1295 1300 1305  
 Ile Arg Met Leu Gly Ala Thr Cys Glu Lys Ser Asn Tyr Asn Leu  
 1310 1315 1320  
 Phe Ile Glu Trp Met Ala Gly Gly Ser Val Ala His Leu Leu Ser  
 1325 1330 1335  
 Lys Tyr Gly Ala Phe Lys Glu Ser Val Val Ile Asn Tyr Thr Glu  
 1340 1345 1350  
 Gln Leu Leu Arg Gly Leu Ser Tyr Leu His Glu Asn Gln Ile Ile  
 1355 1360 1365  
 His Arg Asp Val Lys Gly Ala Asn Leu Leu Ile Asp Ser Thr Gly  
 1370 1375 1380  
 Gln Arg Leu Arg Ile Ala Asp Phe Gly Ala Ala Ala Arg Leu Ala  
 1385 1390 1395  
 Ser Lys Gly Thr Gly Ala Gly Glu Phe Gln Gly Gln Leu Leu Gly  
 1400 1405 1410  
 Thr Ile Ala Phe Met Ala Pro Glu Val Leu Arg Gly Gln Gln Tyr  
 1415 1420 1425  
 Gly Arg Ser Cys Asp Val Trp Ser Val Gly Cys Ala Ile Ile Glu  
 1430 1435 1440  
 Met Ala Cys Ala Lys Pro Pro Trp Asn Ala Glu Lys His Ser Asn  
 1445 1450 1455  
 His Leu Ala Leu Ile Phe Lys Ile Ala Ser Ala Thr Thr Ala Pro  
 1460 1465 1470  
 Ser Ile Pro Ser His Leu Ser Pro Gly Leu Arg Asp Val Ala Leu  
 1475 1480 1485  
 Arg Cys Leu Glu Leu Gln Pro Gln Asp Arg Pro Pro Ser Arg Glu  
 1490 1495 1500  
 Leu Leu Lys His Pro Val Phe Arg Thr Thr Trp  
 1505 1510

&lt;210&gt; 7

&lt;211&gt; 830

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 7482905CD1

&lt;400&gt; 7

Met Lys Ala Glu Gln Met Lys Arg Gln Glu Lys Glu Arg Leu Glu  
 1 5 10 15  
 Arg Ile Asn Arg Ala Arg Glu Gln Gly Trp Arg Asn Val Leu Ser  
 20 25 30  
 Ala Gly Gly Ser Gly Glu Val Lys Ala Pro Phe Leu Gly Ser Gly  
 35 40 45  
 Gly Thr Ile Ala Pro Ser Ser Phe Ser Ser Arg Gly Gln Tyr Glu  
 50 55 60

His Tyr His Ala Ile Phe Asp Gln Met Gln Gln Gln Arg Ala Glu	65	70	75
Asp Asn Glu Ala Lys Trp Lys Arg Glu Ile Tyr Gly Arg Gly Leu	80	85	90
Pro Glu Arg Gln Lys Gly Gln Leu Ala Val Glu Arg Ala Lys Gln	95	100	105
Val Glu Glu Phe Leu Gln Arg Lys Arg Glu Ala Met Gln Asn Lys	110	115	120
Ala Arg Ala Glu Gly His Met Val Tyr Leu Ala Arg Leu Arg Gln	125	130	135
Ile Arg Leu Gln Asn Phe Asn Glu Arg Gln Gln Ile Lys Ala Lys	140	145	150
Leu Arg Gly Glu Lys Lys Glu Ala Asn His Ser Glu Gly Gln Glu	155	160	165
Gly Ser Glu Glu Ala Asp Met Arg Arg Lys Lys Ile Glu Ser Leu	170	175	180
Lys Ala His Ala Asn Ala Arg Ala Ala Val Leu Lys Glu Gln Leu	185	190	195
Glu Arg Lys Arg Lys Glu Ala Tyr Glu Arg Glu Lys Lys Val Trp	200	205	210
Glu Glu His Leu Val Ala Lys Gly Val Lys Ser Ser Asp Val Ser	215	220	225
Pro Pro Leu Gly Gln His Glu Thr Gly Gly Ser Pro Ser Lys Gln	230	235	240
Gln Met Arg Ser Val Ile Ser Val Thr Ser Ala Leu Lys Glu Val	245	250	255
Gly Val Asp Ser Ser Leu Thr Asp Thr Arg Glu Thr Ser Glu Glu	260	265	270
Met Gln Lys Thr Asn Asn Ala Ile Ser Ser Lys Arg Glu Ile Leu	275	280	285
Arg Arg Leu Asn Glu Asn Leu Lys Ala Gln Glu Asp Glu Lys Gly	290	295	300
Lys Gln Asn Leu Ser Asp Thr Phe Glu Ile Asn Val His Glu Asp	305	310	315
Ala Lys Glu His Glu Lys Glu Lys Ser Val Ser Ser Asp Arg Lys	320	325	330
Lys Trp Glu Ala Gly Gly Gln Leu Val Ile Pro Leu Asp Glu Leu	335	340	345
Thr Leu Asp Thr Ser Phe Ser Thr Thr Glu Arg His Thr Val Gly	350	355	360
Glu Val Ile Lys Leu Gly Pro Asn Gly Ser Pro Arg Arg Ala Trp	365	370	375
Gly Lys Ser Pro Thr Asp Ser Val Leu Lys Ile Leu Gly Glu Ala	380	385	390
Glu Leu Gln Leu Gln Thr Glu Leu Leu Glu Asn Thr Thr Ile Arg	395	400	405
Ser Glu Ile Ser Pro Glu Gly Glu Lys Tyr Lys Pro Leu Ile Thr	410	415	420
Gly Glu Lys Lys Val Gln Cys Ile Ser His Glu Ile Asn Pro Ser	425	430	435
Ala Ile Val Asp Ser Pro Val Glu Thr Lys Ser Pro Glu Phe Ser	440	445	450
Glu Ala Ser Pro Gln Met Ser Leu Lys Leu Glu Gly Asn Leu Glu	455	460	465
Glu Pro Asp Asp Leu Glu Thr Glu Ile Leu Gln Glu Pro Ser Gly	470	475	480
Thr Asn Lys Asp Glu Ser Leu Pro Cys Thr Ile Thr Asp Val Trp	485	490	495
Ile Ser Glu Glu Lys Glu Thr Lys Glu Thr Gln Ser Ala Asp Arg	500	505	510
Ile Thr Ile Gln Glu Asn Glu Val Ser Glu Asp Gly Val Ser Ser	515	520	525
Thr Val Asp Gln Leu Ser Asp Ile His Ile Glu Pro Gly Thr Asn			

530	535	540
Asp Ser Gln His Ser Lys Cys Asp Val	Asp Lys Ser Val Gln Pro	
545	550	555
Glu Pro Phe Phe His Lys Val Val His	Ser Glu His Leu Asn Leu	
560	565	570
Val Pro Gln Val Gln Ser Val Gln Cys	Ser Pro Glu Glu Ser Phe	
575	580	585
Ala Phe Arg Ser His Ser His Leu Pro	Pro Lys Asn Lys Asn Lys	
590	595	600
Asn Ser Leu Leu Ile Gly Leu Ser Thr	Gly Leu Phe Asp Ala Asn	
605	610	615
Asn Pro Lys Met Leu Arg Thr Cys Ser	Leu Pro Asp Leu Ser Lys	
620	625	630
Leu Phe Arg Thr Leu Met Asp Val Pro	Thr Val Gly Asp Val Arg	
635	640	645
Gln Asp Asn Leu Glu Ile Asp Glu Ile	Glu Asp Glu Asn Ile Lys	
650	655	660
Glu Gly Pro Ser Asp Ser Glu Asp Ile	Val Phe Glu Glu Thr Asp	
665	670	675
Thr Asp Leu Gln Glu Leu Gln Ala Ser	Met Glu Gln Leu Leu Arg	
680	685	690
Glu Gln Pro Gly Glu Glu Tyr Ser Glu	Glu Glu Glu Ser Val Leu	
695	700	705
Lys Asn Ser Asp Val Glu Pro Thr Ala	Asn Gly Thr Asp Val Ala	
710	715	720
Asp Glu Asp Asp Asn Pro Ser Ser Glu	Ser Ala Leu Asn Glu Glu	
725	730	735
Trp His Ser Asp Asn Ser Asp Gly Glu	Ile Ala Ser Glu Cys Glu	
740	745	750
Cys Asp Ser Val Phe Asn His Leu Glu	Glu Leu Arg Leu His Leu	
755	760	765
Glu Gln Glu Met Gly Phe Glu Lys Phe	Phe Glu Val Tyr Glu Lys	
770	775	780
Ile Lys Ala Ile His Glu Asp Glu Asp	Glu Asn Ile Glu Ile Cys	
785	790	795
Ser Lys Ile Val Gln Asn Ile Leu Gly	Asn Glu His Gln His Leu	
800	805	810
Tyr Ala Lys Ile Leu His Leu Val Met	Ala Asp Gly Ala Tyr Gln	
815	820	825
Glu Asp Asn Asp Glu		
830		

&lt;210&gt; 8

&lt;211&gt; 455

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 7483019CD1

&lt;400&gt; 8

Met Arg Ile Val Cys Leu Val Lys Asn Gln Gln Pro Leu Gly Ala	
1 5 10 15	
Thr Ile Lys Arg His Glu Met Thr Gly Asp Ile Leu Val Ala Arg	
20 25 30	
Ile Ile His Gly Gly Leu Ala Glu Arg Ser Gly Leu Leu Tyr Ala	
35 40 45	
Gly Asp Lys Leu Val Glu Val Asn Gly Val Ser Val Glu Gly Leu	
50 55 60	
Asp Pro Glu Gln Val Ile His Ile Leu Ala Met Ser Arg Gly Thr	
65 70 75	
Ile Met Phe Lys Val Val Pro Val Ser Asp Pro Pro Val Asn Ser	

	80		85		90
Gln Gln Met Val Tyr Val Arg Ala Met Thr Glu Tyr Trp Pro Gln					
	95		100		105
Glu Asp Pro Asp Ile Pro Cys Met Asp Ala Gly Leu Pro Phe Gln					
	110		115		120
Lys Gly Asp Ile Leu Gln Ile Val Asp Gln Asn Asp Ala Leu Trp					
	125		130		135
Trp Gln Ala Arg Lys Ile Ser Asp Pro Ala Thr Cys Ala Gly Leu					
	140		145		150
Val Pro Ser Asn His Leu Leu Lys Arg Lys Gln Arg Glu Phe Trp					
	155		160		165
Trp Ser Gln Pro Tyr Gln Pro His Thr Cys Leu Lys Ser Thr Leu					
	170		175		180
Tyr Lys Glu Glu Phe Val Gly Tyr Gly Gln Lys Phe Phe Ile Ala					
	185		190		195
Gly Phe Arg Arg Ser Met Arg Leu Cys Arg Arg Lys Ser His Leu					
	200		205		210
Ser Pro Leu His Ala Ser Val Cys Cys Thr Gly Ser Cys Tyr Ser					
	215		220		225
Ala Val Gly Ala Pro Tyr Glu Glu Val Val Arg Tyr Gln Arg Arg					
	230		235		240
Pro Ser Asp Lys Tyr Arg Leu Ile Val Leu Met Gly Pro Ser Gly					
	245		250		255
Val Gly Val Asn Glu Leu Arg Arg Gln Leu Ile Glu Phe Asn Pro					
	260		265		270
Ser His Phe Gln Ser Ala Val Pro His Thr Thr Arg Thr Lys Lys					
	275		280		285
Ser Tyr Glu Thr Asn Gly Arg Glu Tyr His Tyr Val Ser Lys Glu					
	290		295		300
Thr Phe Glu Asn Leu Ile Tyr Ser His Arg Met Leu Glu Tyr Gly					
	305		310		315
Glu Tyr Lys Gly His Leu Tyr Gly Thr Ser Val Gly Ala Val Gln					
	320		325		330
Thr Val Leu Val Glu Gly Lys Ile Cys Val Met Asp Leu Glu Pro					
	335		340		345
Gln Asp Ile Gln Gly Val Arg Thr His Glu Leu Lys Pro Tyr Val					
	350		355		360
Ile Phe Ile Lys Pro Ser Asn Met Arg Cys Met Lys Gln Ser Arg					
	365		370		375
Lys Asn Ala Lys Val Ile Thr Asp Tyr Tyr Val Asp Met Lys Phe					
	380		385		390
Lys Asp Glu Asp Leu Gln Glu Met Glu Asn Leu Ala Gln Arg Met					
	395		400		405
Glu Thr Gln Phe Gly Gln Phe Phe Asp His Val Ile Val Asn Asp					
	410		415		420
Ser Leu His Asp Ala Cys Ala Gln Leu Leu Ser Ala Ile Gln Lys					
	425		430		435
Ala Gln Glu Glu Pro Gln Trp Val Pro Ala Thr Trp Ile Ser Ser					
	440		445		450
Asp Thr Glu Ser Gln					
	455				

&lt;210&gt; 9

&lt;211&gt; 1720

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 5455490CD1

&lt;400&gt; 9

Met Met Lys Arg Arg Arg Glu Arg Leu Gly Ala Pro Cys Leu Arg

1	5	10	15
Ile Gln Ile Ser Thr	Leu Cys Arg Gly	Ala Glu Val Asn Gln	His
20	25		30
Met Phe Ser Pro Thr	Ser Ala Pro Ala	Leu Phe Leu Thr	Lys Val
35	40		45
Pro Phe Ser Ala Asp	Cys Ala Leu Ala	Thr Ser Pro Leu	Ala Ile
50	55		60
Phe Leu Asn Pro Arg	Ala His Ser Ser	Pro Gly Thr Pro	Cys Ser
65	70		75
Ser Arg Pro Leu Pro	Trp Ser Cys Arg	Thr Ser Asn Arg	Lys Ser
80	85		90
Leu Ile Val Thr Ser	Ser Thr Ser Pro	Thr Leu Pro Arg	Pro His
95	100		105
Ser Pro Leu His Gly	His Thr Gly Asn	Ser Pro Leu Asp	Ser Pro
110	115		120
Arg Asn Phe Ser Pro	Asn Ala Pro Ala	His Phe Ser Phe	Val Pro
125	130		135
Ala Arg Ser His Ser	His Arg Ala Asp	Arg Thr Asp Gly	Arg Arg
140	145		150
Trp Ser Leu Ala Ser	Leu Pro Ser Ser	Gly Tyr Gly Thr	Asn Thr
155	160		165
Pro Ser Ser Thr Val	Ser Ser Ser Cys	Ser Ser Gln Glu	Lys Leu
170	175		180
His Gln Leu Pro Phe	Gln Pro Thr Ala	Asp Glu Leu His	Phe Leu
185	190		195
Thr Lys His Phe Ser	Thr Glu Ser Val	Pro Asp Glu Glu	Gly Arg
200	205		210
Gln Ser Pro Ala Met	Arg Pro Arg Ser	Arg Ser Leu Ser	Pro Gly
215	220		225
Arg Ser Pro Val Ser	Phe Asp Ser Glu	Ile Ile Met Met	Asn His
230	235		240
Val Tyr Lys Glu Arg	Phe Pro Lys Ala	Thr Ala Gln Met	Glu Glu
245	250		255
Arg Leu Ala Glu Phe	Ile Ser Ser Asn	Thr Pro Asp Ser	Val Leu
260	265		270
Pro Leu Ala Asp Gly	Ala Leu Ser Phe	Ile His His Gln	Val Ile
275	280		285
Glu Met Ala Arg Asp	Cys Leu Asp Lys	Ser Arg Ser Gly	Leu Ile
290	295		300
Thr Ser Gln Tyr Phe	Tyr Glu Leu Gln	Glu Asn Leu Glu	Lys Leu
305	310		315
Leu Gln Asp Ala His	Glu Arg Ser Glu	Ser Ser Glu Val	Ala Phe
320	325		330
Val Met Gln Leu Val	Lys Lys Leu Met	Ile Ile Ile Ala	Arg Pro
335	340		345
Ala Arg Leu Leu Glu	Cys Leu Glu Phe	Asp Pro Glu Glu	Phe Tyr
350	355		360
His Leu Leu Glu Ala	Ala Glu Gly His	Ala Lys Glu Gly	Gln Gly
365	370		375
Ile Lys Cys Asp Ile	Pro Arg Tyr Ile	Val Ser Gln Leu	Gly Leu
380	385		390
Thr Arg Asp Pro Leu	Glu Glu Met Ala	Gln Leu Ser Ser	Cys Asp
395	400		405
Ser Pro Asp Thr Pro	Glu Thr Asp Asp	Ser Ile Glu Gly	His Gly
410	415		420
Ala Ser Leu Pro Ser	Lys Lys Thr Pro	Ser Glu Glu Asp	Phe Glu
425	430		435
Thr Ile Lys Leu Ile	Ser Asn Gly Ala	Tyr Gly Ala Val	Phe Leu
440	445		450
Val Arg His Lys Ser	Thr Arg Gln Arg	Phe Ala Met Lys	Lys Ile
455	460		465
Asn Lys Gln Asn Leu	Ile Leu Arg Asn	Gln Ile Gln Gln	Ala Phe
470	475		480

Val	Glu	Arg	Asp	Ile	Leu	Thr	Phe	Ala	Glu	Asn	Pro	Phe	Val	Val
				485					490					495
Ser	Met	Phe	Cys	Ser	Phe	Asp	Thr	Lys	Arg	His	Leu	Cys	Met	Val
				500					505					510
Met	Glu	Tyr	Val	Glu	Gly	Gly	Asp	Cys	Ala	Thr	Leu	Leu	Lys	Asn
				515					520					525
Ile	Gly	Ala	Leu	Pro	Val	Asp	Met	Val	Arg	Leu	Tyr	Phe	Ala	Glu
				530					535					540
Thr	Val	Leu	Ala	Leu	Glu	Tyr	Leu	His	Asn	Tyr	Gly	Ile	Val	His
				545					550					555
Arg	Asp	Leu	Lys	Pro	Asp	Asn	Leu	Leu	Ile	Thr	Ser	Met	Gly	His
				560					565					570
Ile	Lys	Leu	Thr	Asp	Phe	Gly	Leu	Ser	Lys	Ile	Gly	Leu	Met	Ser
				575					580					585
Leu	Thr	Thr	Asn	Leu	Tyr	Glu	Gly	His	Ile	Glu	Lys	Asp	Ala	Arg
				590					595					600
Glu	Phe	Leu	Asp	Lys	Gln	Val	Cys	Gly	Thr	Pro	Glu	Tyr	Ile	Ala
				605					610					615
Pro	Glu	Val	Ile	Leu	Arg	Gln	Gly	Tyr	Gly	Lys	Pro	Val	Asp	Trp
				620					625					630
Trp	Ala	Met	Gly	Ile	Ile	Leu	Tyr	Glu	Phe	Leu	Val	Gly	Cys	Val
				635					640					645
Pro	Phe	Phe	Gly	Asp	Thr	Pro	Glu	Glu	Leu	Phe	Gly	Gln	Val	Ile
				650					655					660
Ser	Asp	Glu	Ile	Val	Trp	Pro	Glu	Gly	Asp	Glu	Ala	Leu	Pro	Pro
				665					670					675
Asp	Ala	Gln	Asp	Leu	Thr	Ser	Lys	Leu	Leu	His	Gln	Asn	Pro	Leu
				680					685					690
Glu	Arg	Leu	Gly	Thr	Gly	Ser	Ala	Tyr	Glu	Val	Lys	Gln	His	Pro
				695					700					705
Phe	Phe	Thr	Gly	Leu	Asp	Trp	Thr	Gly	Leu	Leu	Arg	Gln	Lys	Ala
				710					715					720
Glu	Phe	Ile	Pro	Gln	Leu	Glu	Ser	Glu	Asp	Asp	Thr	Ser	Tyr	Phe
				725					730					735
Asp	Thr	Arg	Ser	Glu	Arg	Tyr	His	His	Met	Asp	Ser	Glu	Asp	Glu
				740					745					750
Glu	Glu	Val	Ser	Glu	Asp	Gly	Cys	Leu	Glu	Ile	Arg	Gln	Phe	Ser
				755					760					765
Ser	Cys	Ser	Pro	Arg	Phe	Asn	Lys	Val	Tyr	Ser	Ser	Met	Glu	Arg
				770					775					780
Leu	Ser	Leu	Leu	Glu	Glu	Arg	Arg	Thr	Pro	Pro	Pro	Thr	Lys	Arg
				785					790					795
Ser	Leu	Ser	Glu	Glu	Lys	Glu	Asp	His	Ser	Asp	Gly	Leu	Ala	Gly
				800					805					810
Leu	Lys	Gly	Arg	Asp	Arg	Ser	Trp	Val	Ile	Gly	Ser	Pro	Glu	Ile
				815					820					825
Leu	Arg	Lys	Arg	Leu	Ser	Val	Ser	Glu	Ser	Ser	His	Thr	Glu	Ser
				830					835					840
Asp	Ser	Ser	Pro	Pro	Met	Thr	Val	Arg	Arg	Arg	Cys	Ser	Gly	Leu
				845					850					855
Leu	Asp	Ala	Pro	Arg	Phe	Pro	Glu	Gly	Pro	Glu	Glu	Ala	Ser	Ser
				860					865					870
Thr	Leu	Arg	Arg	Gln	Pro	Gln	Glu	Gly	Ile	Trp	Val	Leu	Thr	Pro
				875					880					885
Pro	Ser	Gly	Glu	Gly	Val	Ser	Gly	Pro	Val	Thr	Glu	His	Ser	Gly
				890					895					900
Glu	Gln	Arg	Pro	Lys	Leu	Asp	Glu	Glu	Ala	Val	Gly	Arg	Ser	Ser
				905					910					915
Gly	Ser	Ser	Pro	Ala	Met	Glu	Thr	Arg	Gly	Arg	Gly	Thr	Ser	Gln
				920					925					930
Leu	Ala	Glu	Gly	Ala	Thr	Ala	Lys	Ala	Ile	Ser	Asp	Leu	Ala	Val
				935					940					945
Arg	Arg	Ala	Arg	His	Arg	Leu	Leu	Ser	Gly	Asp	Ser	Thr	Glu	Lys

Arg Thr Ala Arg	950	955	960
Pro Val Asn Lys Val	965	Ile Lys Ser Ala Ser	Ala
Thr Ala Leu Ser	980	Glu His His Thr Cys Ser	975
Leu Ile Pro Ser	985	His His Thr Cys Ser	990
Pro Leu Ala Ser	995	Pro Met Ser Pro His Ser Gln Ser Ser Asn Pro	1005
Ser Ser Arg Asp	1010	1000	1020
Ser Ser Pro Ser Arg Asp	1015	Phe Leu Pro Ala Leu	1035
Gly Ser Met Arg Pro	1025	1015	1050
Pro Ile Ile Ile His Arg Ala Gly Lys Lys	1030	1040	1065
Tyr Gly Phe Thr Leu Arg Ala Ile Arg Val Tyr Met Gly Asp Ser	1045	1055	1080
Asp Val Tyr Thr Val His His Met Val Trp His Val Glu Asp Gly	1060	1070	1095
Gly Pro Ala Ser Glu Ala Gly Leu Arg Gln Gly Asp Leu Ile Thr	1075	1085	1110
His Val Asn Gly Glu Pro Val His Gly Leu Val His Thr Glu Val	1090	1100	1125
Val Glu Leu Ile Leu Lys Ser Gly Asn Lys Val Ala Ile Ser Thr	1105	1115	1140
Thr Pro Leu Glu Asn Thr Ser Ile Lys Val Gly Pro Ala Arg Lys	1120	1130	1155
Gly Ser Tyr Lys Ala Lys Met Ala Arg Arg Ser Lys Arg Ser Arg	1135	1145	1170
Gly Lys Asp Gly Gln Glu Ser Arg Lys Arg Ser Ser Leu Phe Arg	1150	1160	1185
Lys Ile Thr Lys Gln Ala Ser Leu Leu His Thr Ser Arg Ser Leu	1165	1175	1200
Ser Ser Leu Asn Arg Ser Leu Ser Ser Gly Glu Ser Gly Pro Gly	1180	1190	1215
Ser Pro Thr His Ser His Ser Leu Ser Pro Arg Ser Pro Thr Gln	1195	1205	1230
Gly Tyr Arg Val Thr Pro Asp Ala Val His Ser Val Gly Gly Asn	1210	1220	1245
Ser Ser Gln Ser Ser Ser Pro Ser Ser Ser Val Pro Ser Ser Pro	1225	1235	1260
Ala Gly Ser Gly His Thr Arg Pro Ser Ser Leu His Gly Leu Ala	1240	1250	1275
Pro Lys Leu Gln Arg Gln Tyr Arg Ser Pro Arg Arg Lys Ser Ala	1255	1265	1290
Gly Ser Ile Pro Leu Ser Pro Leu Ala His Thr Pro Ser Pro Pro	1270	1280	1305
Pro Pro Thr Ala Ser Pro Gln Arg Ser Pro Ser Pro Leu Ser Gly	1285	1295	1320
His Val Ala Gln Ala Phe Pro Thr Lys Leu His Leu Ser Pro Pro	1300	1310	1335
Leu Gly Arg Gln Leu Ser Arg Pro Lys Ser Ala Glu Pro Pro Arg	1315	1325	1350
Ser Pro Leu Leu Lys Arg Val Gln Ser Ala Glu Lys Leu Ala Ala	1330	1340	1365
Ala Leu Ala Ala Ser Glu Lys Lys Leu Ala Thr Ser Arg Lys His	1345	1355	1380
Ser Leu Asp Leu Pro His Ser Glu Leu Lys Lys Glu Leu Pro Pro	1360	1370	1395
Arg Glu Val Ser Pro Leu Glu Val Val Gly Ala Arg Ser Val Leu	1375	1385	1410
Ser Gly Lys Gly Ala Leu Pro Gly Lys Gly Val Leu Gln Pro Ala	1390	1400	1425
Pro Ser Arg Ala Leu Gly Thr Leu Arg Gln Asp Arg Ala Glu Arg	1405	1415	
Arg Glu Ser Leu Gln Lys Gln Glu Ala Ile Arg Glu Val Asp Ser	1420		

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Ser Glu Asp Asp Thr Glu Glu Gly Pro Glu Asn Ser Gln Gly Ala
      1430                      1435                      1440
Gln Glu Leu Ser Leu Ala Pro His Pro Glu Val Ser Gln Ser Val
      1445                      1450                      1455
Ala Pro Lys Gly Ala Gly Glu Ser Gly Glu Glu Asp Pro Phe Pro
      1460                      1465                      1470
Ser Arg Asp Pro Arg Ser Leu Gly Pro Met Val Pro Ser Leu Leu
      1475                      1480                      1485
Thr Gly Ile Thr Leu Gly Pro Pro Arg Met Glu Ser Pro Ser Gly
      1490                      1495                      1500
Pro His Arg Arg Leu Gly Ser Pro Gln Ala Ile Glu Glu Ala Ala
      1505                      1510                      1515
Ser Ser Ser Ser Ala Gly Pro Asn Leu Gly Gln Ser Gly Ala Thr
      1520                      1525                      1530
Asp Pro Ile Pro Pro Glu Gly Cys Trp Lys Ala Gln His Leu His
      1535                      1540                      1545
Thr Gln Ala Leu Thr Ala Leu Ser Pro Ser Thr Ser Gly Leu Thr
      1550                      1555                      1560
Pro Thr Ser Ser Cys Ser Pro Pro Ser Ser Thr Ser Gly Lys Leu
      1565                      1570                      1575
Ser Met Trp Ser Trp Lys Ser Leu Ile Glu Gly Pro Asp Arg Ala
      1580                      1585                      1590
Ser Pro Ser Arg Lys Ala Thr Met Ala Gly Gly Leu Ala Asn Leu
      1595                      1600                      1605
Gln Asp Leu Glu Asn Thr Thr Pro Ala Gln Pro Lys Asn Leu Ser
      1610                      1615                      1620
Pro Arg Glu Gln Gly Lys Thr Gln Pro Pro Ser Ala Pro Arg Leu
      1625                      1630                      1635
Ala His Pro Ser Tyr Glu Asp Pro Ser Gln Gly Trp Leu Trp Glu
      1640                      1645                      1650
Ser Glu Cys Ala Gln Ala Val Lys Glu Asp Pro Ala Leu Ser Ile
      1655                      1660                      1665
Thr Gln Val Pro Asp Ala Ser Gly Asp Arg Arg Gln Asp Val Pro
      1670                      1675                      1680
Cys Arg Gly Cys Pro Leu Thr Gln Lys Ser Glu Pro Ser Leu Arg
      1685                      1690                      1695
Arg Gly Gln Glu Pro Gly Gly His Gln Lys His Arg Asp Leu Ala
      1700                      1705                      1710
Leu Val Pro Asp Glu Leu Leu Lys Gln Thr
      1715                      1720

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&lt;210&gt; 10

&lt;211&gt; 449

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 5547067CD1

&lt;400&gt; 10

```

Met Leu Met Gly Phe Cys Arg Leu Glu Glu Ala Gly Leu Val Ser
  1           5           10           15
Arg Ser Ile Arg Glu Arg Asn Cys Leu Tyr Asn Trp Asp Ser Arg
      20           25           30
Phe Ser Arg Glu Arg Arg Gln Arg Leu Gly Met Gly Ala Val Ser
      35           40           45
Cys Arg Gln Gly Gln His Thr Gln Gln Gly Glu His Thr Arg Val
      50           55           60
Ala Val Pro His Lys Gly Gly Asn Ile Arg Gly Pro Trp Ala Arg
      65           70           75
Gly Trp Lys Ser Leu Trp Thr Gly Leu Gly Thr Ile Arg Ser Asp
      80           85           90

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WO 02/46384

Leu Glu Glu Leu Trp Glu Leu Arg Gly His His Tyr Leu His Gln  
 95 100 105  
 Glu Ser Leu Lys Pro Ala Pro Val Leu Val Glu Lys Pro Leu Pro  
 110 115 120  
 Glu Trp Pro Val Pro Gln Phe Ile Asn Leu Phe Leu Pro Glu Phe  
 125 130 135  
 Pro Ile Arg Pro Ile Arg Gly Gln Gln Gln Leu Lys Ile Leu Gly  
 140 145 150  
 Leu Val Ala Lys Gly Ser Phe Gly Thr Val Leu Lys Val Leu Asp  
 155 160 165  
 Cys Thr Gln Lys Ala Val Phe Ala Val Lys Val Val Pro Lys Val  
 170 175 180  
 Lys Val Leu Gln Arg Asp Thr Val Arg Gln Cys Lys Glu Glu Val  
 185 190 195  
 Ser Ile Gln Arg Gln Ile Asn His Pro Phe Val His Ser Leu Gly  
 200 205 210  
 Asp Ser Trp Gln Gly Lys Arg His Leu Phe Ile Met Cys Ser Tyr  
 215 220 225  
 Cys Ser Thr Asp Leu Tyr Ser Leu Trp Ser Ala Val Gly Cys Phe  
 230 235 240  
 Pro Glu Ala Ser Ile Arg Leu Phe Ala Ala Glu Leu Val Leu Val  
 245 250 255  
 Leu Cys Tyr Leu His Asp Leu Gly Ile Met His Arg Asp Val Lys  
 260 265 270  
 Met Glu Asn Ile Leu Leu Asp Glu Arg Gly His Leu Lys Leu Thr  
 275 280 285  
 Asp Phe Gly Leu Ser Arg His Val Pro Gln Gly Ala Gln Ala Tyr  
 290 295 300  
 Thr Ile Cys Gly Thr Leu Gln Tyr Met Ala Pro Glu Val Leu Ser  
 305 310 315  
 Gly Gly Pro Tyr Asn His Ala Ala Asp Trp Trp Ser Leu Gly Val  
 320 325 330  
 Leu Leu Phe Ser Leu Ala Thr Gly Lys Phe Pro Val Ala Ala Glu  
 335 340 345  
 Arg Asp His Val Ala Met Leu Ala Ser Val Thr His Ser Asp Ser  
 350 355 360  
 Glu Ile Pro Ala Ser Leu Asn Gln Gly Leu Ser Leu Leu Leu His  
 365 370 375  
 Glu Leu Leu Cys Gln Asn Pro Leu His Arg Leu Arg Tyr Leu His  
 380 385 390  
 His Phe Gln Val His Pro Phe Phe Arg Gly Val Ala Phe Asp Pro  
 395 400 405  
 Glu Leu Leu Gln Lys Gln Pro Val Asn Phe Val Thr Glu Thr Gln  
 410 415 420  
 Ala Thr Gln Pro Ser Ser Ala Glu Thr Met Pro Phe Asp Asp Phe  
 425 430 435  
 Asp Cys Asp Leu Glu Ser Phe Leu Leu Tyr Pro Ile Pro Ala  
 440 445

&lt;210&gt; 11

&lt;211&gt; 358

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 71675660CD1

&lt;400&gt; 11

Met Asp Asp Ala Thr Val Leu Arg Lys Lys Gly Tyr Ile Val Gly  
 1 5 10 15  
 Ile Asn Leu Gly Lys Gly Ser Tyr Ala Lys Val Lys Ser Ala Tyr  
 20 25 30

```

Ser Glu Arg Leu Lys Phe Asn Val Ala Val Lys Ile Ile Asp Arg
      35              40              45
Lys Lys Thr Pro Thr Asp Phe Val Glu Arg Phe Leu Pro Arg Glu
      50              55              60
Met Asp Ile Leu Ala Thr Val Asn His Gly Ser Ile Ile Lys Thr
      65              70              75
Tyr Glu Ile Phe Glu Thr Ser Asp Gly Arg Ile Tyr Ile Ile Met
      80              85              90
Glu Leu Gly Val Gln Gly Asp Leu Leu Glu Phe Ile Lys Cys Gln
      95              100             105
Gly Ala Leu His Glu Asp Val Ala Arg Lys Met Phe Arg Gln Leu
     110             115             120
Ser Ser Ala Val Lys Tyr Cys His Asp Leu Asp Ile Val His Arg
     125             130             135
Asp Leu Lys Cys Glu Asn Leu Leu Leu Asp Lys Asp Phe Asn Ile
     140             145             150
Lys Leu Ser Asp Phe Gly Phe Ser Lys Arg Cys Leu Arg Asp Ser
     155             160             165
Asn Gly Arg Ile Ile Leu Ser Lys Thr Phe Cys Gly Ser Ala Ala
     170             175             180
Tyr Ala Ala Pro Glu Val Leu Gln Ser Ile Pro Tyr Gln Pro Lys
     185             190             195
Val Tyr Asp Ile Trp Ser Leu Gly Val Ile Leu Tyr Ile Met Val
     200             205             210
Cys Gly Ser Met Pro Tyr Asp Asp Ser Asp Ile Arg Lys Met Leu
     215             220             225
Arg Ile Gln Lys Glu His Arg Val Asp Phe Pro Arg Ser Lys Asn
     230             235             240
Leu Thr Cys Glu Cys Lys Asp Leu Ile Tyr Arg Met Leu Gln Pro
     245             250             255
Asp Val Ser Gln Arg Leu His Ile Asp Glu Ile Leu Ser His Ser
     260             265             270
Trp Leu Gln Pro Pro Lys Pro Lys Ala Met Ser Ser Ala Ser Phe
     275             280             285
Lys Arg Glu Gly Glu Gly Lys Tyr Arg Ala Glu Cys Lys Leu Asp
     290             295             300
Thr Lys Thr Gly Leu Arg Pro Asp His Arg Pro Asp His Lys Leu
     305             310             315
Gly Ala Lys Thr Gln His Arg Leu Leu Val Val Pro Glu Asn Glu
     320             325             330
Asn Arg Met Glu Asp Arg Leu Ala Glu Thr Ser Arg Ala Lys Asp
     335             340             345
His His Ile Ser Gly Ala Glu Val Gly Lys Ala Ser Thr
     350             355

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&lt;210&gt; 12

&lt;211&gt; 358

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 71678683CD1

&lt;400&gt; 12

```

Met Asp Asp Ala Thr Val Leu Arg Lys Lys Gly Tyr Ile Val Gly
  1              5              10              15
Ile Asn Leu Gly Lys Gly Ser Tyr Ala Lys Val Lys Ser Ala Tyr
      20              25              30
Ser Glu Arg Leu Lys Phe Asn Val Ala Val Lys Ile Ile Asp Arg
      35              40              45
Lys Lys Thr Pro Thr Asp Phe Val Glu Arg Phe Leu Pro Arg Glu
      50              55              60

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Met	Asp	Ile	Leu	Ala	Thr	Val	Asn	His	Gly	Ser	Ile	Ile	Lys	Thr	
				65					70					75	
Tyr	Glu	Ile	Phe	Glu	Thr	Ser	Asp	Gly	Arg	Ile	Tyr	Ile	Ile	Met	
				80					85					90	
Glu	Leu	Gly	Val	Gln	Gly	Asp	Leu	Leu	Glu	Phe	Ile	Lys	Cys	Gln	
				95					100					105	
Gly	Ala	Leu	His	Glu	Asp	Val	Ala	Arg	Lys	Met	Phe	Arg	Gln	Leu	
				110					115					120	
Ser	Ser	Ala	Val	Lys	Tyr	Cys	His	Asp	Leu	Asp	Ile	Val	His	Arg	
				125					130					135	
Asp	Leu	Lys	Cys	Glu	Asn	Leu	Leu	Leu	Asp	Lys	Asp	Phe	Asn	Ile	
				140					145					150	
Lys	Leu	Ser	Asp	Phe	Gly	Phe	Ser	Lys	Arg	Cys	Leu	Arg	Asp	Ser	
				155					160					165	
Asn	Gly	Arg	Ile	Ile	Leu	Ser	Lys	Thr	Phe	Cys	Gly	Ser	Ala	Ala	
				170					175					180	
Tyr	Ala	Ala	Pro	Glu	Val	Leu	Gln	Ser	Ile	Pro	Tyr	Gln	Pro	Lys	
				185					190					195	
Val	Tyr	Asp	Ile	Trp	Ser	Leu	Gly	Val	Ile	Leu	Tyr	Ile	Met	Val	
				200					205					210	
Cys	Gly	Ser	Met	Pro	Tyr	Asp	Asp	Ser	Asp	Ile	Arg	Lys	Met	Leu	
				215					220					225	
Arg	Ile	Gln	Lys	Glu	His	Arg	Val	Asp	Phe	Pro	Arg	Ser	Lys	Asn	
				230					235					240	
Leu	Thr	Cys	Glu	Cys	Lys	Asp	Leu	Ile	Tyr	Arg	Met	Leu	Gln	Pro	
				245					250					255	
Asp	Val	Ser	Gln	Arg	Leu	His	Ile	Asp	Glu	Ile	Leu	Ser	His	Ser	
				260					265					270	
Trp	Leu	Gln	Pro	Pro	Lys	Pro	Lys	Ala	Thr	Ser	Ser	Ala	Ser	Phe	
				275					280					285	
Lys	Arg	Glu	Gly	Glu	Gly	Lys	Tyr	Arg	Ala	Glu	Cys	Lys	Leu	Asp	
				290					295					300	
Thr	Lys	Thr	Gly	Leu	Arg	Pro	Asp	His	Arg	Pro	Asp	His	Lys	Leu	
				305					310					315	
Gly	Ala	Lys	Thr	Gln	His	Arg	Leu	Leu	Val	Val	Pro	Glu	Asn	Glu	
				320					325					330	
Asn	Arg	Met	Glu	Asp	Arg	Leu	Ala	Glu	Thr	Ser	Arg	Ala	Lys	Asp	
				335					340					345	
His	His	Ile	Ser	Gly	Ala	Glu	Val	Gly	Lys	Ala	Ser	Thr			
				350					355						

&lt;210&gt; 13

&lt;211&gt; 929

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 7474567CD1

&lt;400&gt; 13

Met	Glu	Ser	Met	Leu	Asn	Lys	Leu	Lys	Ser	Thr	Val	Thr	Lys	Val	
1				5					10					15	
Thr	Ala	Asp	Val	Thr	Ser	Ala	Val	Met	Gly	Asn	Pro	Val	Thr	Arg	
				20					25					30	
Glu	Phe	Asp	Val	Gly	Arg	His	Ile	Ala	Ser	Gly	Gly	Asn	Gly	Leu	
				35					40					45	
Ala	Trp	Lys	Ile	Phe	Asn	Gly	Thr	Lys	Lys	Ser	Thr	Lys	Gln	Glu	
				50					55					60	
Val	Ala	Val	Phe	Val	Phe	Asp	Lys	Lys	Leu	Ile	Asp	Lys	Tyr	Gln	
				65					70					75	
Lys	Phe	Glu	Lys	Asp	Gln	Ile	Ile	Asp	Ser	Leu	Lys	Arg	Gly	Val	
				80					85					90	

Gln	Gln	Leu	Thr	Arg	Leu	Arg	His	Pro	Arg	Leu	Leu	Thr	Val	Gln
				95					100					105
His	Pro	Leu	Glu	Glu	Ser	Arg	Asp	Cys	Leu	Ala	Phe	Cys	Thr	Glu
				110					115					120
Pro	Val	Phe	Ala	Ser	Leu	Ala	Asn	Val	Leu	Gly	Asn	Trp	Glu	Asn
				125					130					135
Leu	Pro	Ser	Pro	Ile	Ser	Pro	Asp	Ile	Lys	Asp	Tyr	Lys	Leu	Tyr
				140					145					150
Asp	Val	Glu	Thr	Lys	Tyr	Gly	Leu	Leu	Gln	Val	Ser	Glu	Gly	Leu
				155					160					165
Ser	Phe	Leu	His	Ser	Ser	Val	Lys	Met	Val	His	Gly	Asn	Ile	Thr
				170					175					180
Pro	Glu	Asn	Ile	Ile	Leu	Asn	Lys	Ser	Gly	Ala	Trp	Lys	Ile	Met
				185					190					195
Gly	Phe	Asp	Phe	Cys	Val	Ser	Ser	Thr	Asn	Pro	Ser	Glu	Gln	Glu
				200					205					210
Pro	Lys	Phe	Pro	Cys	Lys	Glu	Trp	Asp	Pro	Asn	Leu	Pro	Ser	Leu
				215					220					225
Cys	Leu	Pro	Asn	Pro	Glu	Tyr	Leu	Ala	Pro	Glu	Tyr	Ile	Leu	Ser
				230					235					240
Val	Ser	Cys	Glu	Thr	Ala	Ser	Asp	Met	Tyr	Ser	Leu	Gly	Thr	Val
				245					250					255
Met	Tyr	Ala	Val	Phe	Asn	Lys	Gly	Lys	Pro	Ile	Phe	Glu	Val	Asn
				260					265					270
Lys	Gln	Asp	Ile	Tyr	Lys	Ser	Phe	Ser	Arg	Gln	Leu	Asp	Gln	Leu
				275					280					285
Ser	Arg	Leu	Gly	Ser	Ser	Ser	Leu	Thr	Asn	Ile	Pro	Glu	Glu	Val
				290					295					300
Arg	Glu	His	Val	Lys	Leu	Leu	Leu	Asn	Val	Thr	Pro	Thr	Val	Arg
				305					310					315
Pro	Asp	Ala	Asp	Gln	Met	Thr	Lys	Ile	Pro	Phe	Phe	Asp	Asp	Val
				320					325					330
Gly	Ala	Val	Thr	Leu	Gln	Tyr	Phe	Asp	Thr	Leu	Phe	Gln	Arg	Asp
				335					340					345
Asn	Leu	Gln	Lys	Ser	Gln	Phe	Phe	Lys	Gly	Leu	Pro	Lys	Val	Leu
				350					355					360
Pro	Lys	Leu	Pro	Lys	Arg	Val	Ile	Val	Gln	Arg	Ile	Leu	Pro	Cys
				365					370					375
Leu	Thr	Ser	Glu	Phe	Val	Asn	Pro	Asp	Met	Val	Pro	Phe	Val	Leu
				380					385					390
Pro	Asn	Val	Leu	Leu	Ile	Ala	Glu	Glu	Cys	Thr	Lys	Glu	Glu	Tyr
				395					400					405
Val	Lys	Leu	Ile	Leu	Pro	Glu	Leu	Gly	Pro	Val	Phe	Lys	Gln	Gln
				410					415					420
Glu	Pro	Ile	Gln	Ile	Leu	Leu	Ile	Phe	Leu	Gln	Lys	Met	Asp	Leu
				425					430					435
Leu	Leu	Thr	Lys	Thr	Pro	Pro	Asp	Glu	Ile	Lys	Asn	Ser	Val	Leu
				440					445					450
Pro	Met	Val	Tyr	Arg	Ala	Leu	Glu	Ala	Pro	Ser	Ile	Gln	Ile	Gln
				455					460					465
Glu	Leu	Cys	Leu	Asn	Ile	Ile	Pro	Thr	Phe	Ala	Asn	Leu	Ile	Asp
				470					475					480
Tyr	Pro	Ser	Met	Lys	Asn	Ala	Leu	Ile	Pro	Arg	Ile	Lys	Asn	Ala
				485					490					495
Cys	Leu	Gln	Thr	Ser	Ser	Leu	Ala	Val	Arg	Val	Asn	Ser	Leu	Val
				500					505					510
Cys	Leu	Gly	Lys	Ile	Leu	Glu	Tyr	Leu	Asp	Lys	Trp	Phe	Val	Leu
				515					520					525
Asp	Asp	Ile	Leu	Pro	Phe	Leu	Gln	Gln	Ile	Pro	Ser	Lys	Glu	Pro
				530					535					540
Ala	Val	Leu	Met	Gly	Ile	Leu	Gly	Ile	Tyr	Lys	Cys	Thr	Phe	Thr
				545					550					555
His	Lys	Lys	Leu	Gly	Ile	Thr	Lys	Glu	Gln	Leu	Ala	Gly	Lys	Val

Leu Pro His Leu	560	Ile Pro Leu Ser Ile	565	Glu Asn Asn Leu Asn	570
Asn Gln Phe Asn	575	Ser Phe Ile Ser Val	580	Ile Lys Glu Met Leu	585
Arg Leu Glu Ser	590	Glu His Lys Thr Lys	595	Leu Glu Gln Leu His	600
Met Gln Glu Gln	605	Gln Lys Ser Leu Asp	610	Ile Gly Asn Gln Met	615
Val Ser Glu Glu	620	Met Lys Val Thr Asn	625	Ile Gly Asn Gln Gln	630
Asp Lys Val Phe	635	Asn Asn Ile Gly Ala	640	Asp Leu Leu Thr Gly	645
Glu Ser Glu Asn	650	Lys Glu Asp Gly Leu	655	Gln Asn Lys His Lys	660
Ala Ser Leu Thr	665	Leu Glu Glu Lys Gln	670	Lys Leu Ala Lys Glu	675
Glu Gln Ala Gln	680	Lys Leu Lys Ser Gln	685	Gln Pro Leu Lys Pro	690
Val His Thr Pro	695	Val Ala Thr Val Lys	700	Gln Thr Lys Asp Leu	705
Asp Thr Leu Met	710	Asp Asn Met Ser Ser	715	Leu Thr Ser Leu Ser	720
Ser Thr Pro Lys	725	Ser Ser Ala Ser Ser	730	Thr Phe Thr Ser Val	735
Ser Met Gly Ile	740	Gly Met Met Phe Ser	745	Thr Pro Thr Asp Asn	750
Lys Arg Asn Leu	755	Thr Asn Gly Leu Asn	760	Ala Asn Met Gly Phe	765
Thr Ser Gly Phe	770	Asn Met Pro Val Asn	775	Thr Asn Gln Asn Phe	780
Ser Ser Pro Ser	785	Thr Val Gly Val Thr	790	Lys Met Thr Leu Gly	795
Pro Pro Thr Leu	800	Pro Asn Phe Asn Ala	805	Leu Ser Val Pro Pro	810
Gly Ala Lys Gln	815	Thr Gln Gln Arg Pro	820	Thr Asp Met Ser Ala	825
Asn Asn Leu Phe	830	Gly Pro Gln Lys Pro	835	Lys Val Ser Met Asn	840
Leu Ser Gln Gln	845	Lys Pro Asn Gln Trp	850	Leu Asn Gln Phe Val	855
Pro Gln Gly Ser	860	Pro Thr Met Gly Ser	865	Ser Val Met Gly Thr	870
Met Asn Val Ile	875	Gly Gln Ser Ala Phe	880	Ser Val Met Gly Thr	885
Phe Phe Asn Pro	890	Gln Asn Phe Ala Gln	895	Gly Met Gln Gly Asn	900
Asn Ser Ser Ser	905	Ala Ser Asn Asp Leu	910	Pro Pro Thr Thr Met	915
	920		925	Lys Asp Leu Phe Gly	

&lt;210&gt; 14

&lt;211&gt; 523

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 3838946CD1

&lt;400&gt; 14

Met Ala Ala Ala	Leu Gln Val Leu	Pro Arg Leu Ala	Arg Ala Pro
1	5	10	15
Leu His Pro Leu	Leu Trp Arg Gly	Ser Val Ala Arg	Leu Ala Ser

	20		25		30
Ser Met Ala Leu	Ala Glu Gln Ala Arg	Gln Leu Phe Glu Ser	Ala		
	35		40		45
Val Gly Ala Val	Leu Pro Gly Pro Met	Leu His Arg Ala Leu	Ser		
	50		55		60
Leu Asp Pro Gly	Gly Arg Gln Leu Lys	Val Arg Asp Arg Asn	Phe		
	65		70		75
Gln Leu Arg Gln	Asn Leu Tyr Leu Val	Gly Phe Gly Lys Ala	Val		
	80		85		90
Leu Gly Met Ala	Ala Ala Ala Glu Glu	Leu Leu Gly Gln His	Leu		
	95		100		105
Val Gln Gly Val	Ile Ser Val Pro Lys	Gly Ile Arg Ala Ala	Met		
	110		115		120
Glu Arg Ala Gly	Lys Gln Glu Met Leu	Leu Lys Pro His Ser	Arg		
	125		130		135
Val Gln Val Phe	Glu Gly Ala Glu Asp	Asn Leu Pro Asp Arg	Asp		
	140		145		150
Ala Leu Arg Ala	Ala Leu Ala Ile Gln	Gln Leu Ala Glu Gly	Leu		
	155		160		165
Thr Ala Asp Asp	Leu Leu Leu Val Leu	Ile Ser Gly Gly Gly	Ser		
	170		175		180
Ala Leu Leu Pro	Ala Pro Ile Pro Pro	Val Thr Leu Glu Glu	Lys		
	185		190		195
Gln Thr Leu Thr	Arg Leu Leu Ala Ala	Arg Gly Ala Thr Ile	Gln		
	200		205		210
Glu Leu Asn Thr	Ile Arg Lys Ala Leu	Ser Gln Leu Lys Gly	Gly		
	215		220		225
Gly Leu Ala Gln	Ala Ala Tyr Pro Ala	Gln Val Val Ser Leu	Ile		
	230		235		240
Leu Ser Asp Val	Val Gly Asp Pro Val	Glu Val Ile Ala Ser	Gly		
	245		250		255
Pro Thr Val Ala	Ser Ser His Asn Val	Gln Asp Cys Leu His	Ile		
	260		265		270
Leu Asn Arg Tyr	Gly Leu Arg Ala Ala	Leu Pro Arg Ser Val	Lys		
	275		280		285
Thr Val Leu Ser	Arg Ala Asp Ser Asp	Pro His Gly Pro His	Thr		
	290		295		300
Cys Gly His Val	Leu Asn Val Ile Ile	Gly Ser Asn Val Leu	Ala		
	305		310		315
Leu Ala Glu Ala	Gln Arg Gln Ala Glu	Ala Leu Gly Tyr Gln	Ala		
	320		325		330
Val Val Leu Ser	Ala Ala Met Gln Gly	Asp Val Lys Ser Met	Ala		
	335		340		345
Gln Phe Tyr Gly	Leu Leu Ala His Val	Ala Arg Thr Arg Leu	Thr		
	350		355		360
Pro Ser Met Ala	Gly Ala Ser Val Glu	Glu Asp Ala Gln Leu	His		
	365		370		375
Glu Leu Ala Ala	Glu Leu Gln Ile Pro	Asp Leu Gln Leu Glu	Glu		
	380		385		390
Ala Leu Glu Thr	Met Ala Trp Gly Arg	Gly Pro Val Cys Leu	Leu		
	395		400		405
Ala Gly Gly Glu	Pro Thr Val Gln Leu	Gln Gly Ser Gly Arg	Gly		
	410		415		420
Gly Arg Asn Gln	Glu Leu Ala Leu Arg	Val Gly Ala Glu Leu	Arg		
	425		430		435
Arg Trp Pro Leu	Gly Pro Ile Asp Val	Leu Phe Leu Ser Gly	Gly		
	440		445		450
Thr Asp Gly Gln	Asp Gly Pro Thr Glu	Ala Ala Gly Ala Trp	Val		
	455		460		465
Thr Pro Glu Leu	Ala Ser Gln Ala Ala	Ala Glu Gly Leu Asp	Ile		
	470		475		480
Ala Thr Phe Leu	Ala His Asn Asp Ser	His Thr Phe Phe Cys	Cys		
	485		490		495

Leu	Gln	Gly	Gly	Ala	His	Leu	Leu	His	Thr	Gly	Met	Thr	Gly	Thr
				500					505					510
Asn	Val	Met	Asp	Thr	His	Leu	Leu	Phe	Leu	Arg	Pro	Arg		
				515					520					

&lt;210&gt; 15

&lt;211&gt; 459

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 72001176CD1

&lt;400&gt; 15

Met	Asp	His	Pro	Ser	Arg	Glu	Lys	Asp	Glu	Arg	Gln	Arg	Thr	Thr
1				5					10					15
Lys	Pro	Met	Ala	Gln	Arg	Ser	Ala	His	Cys	Ser	Arg	Pro	Ser	Gly
				20					25					30
Ser	Ser	Ser	Ser	Ser	Gly	Val	Leu	Met	Val	Gly	Pro	Asn	Phe	Arg
				35					40					45
Val	Gly	Lys	Lys	Ile	Gly	Cys	Gly	Asn	Phe	Gly	Glu	Leu	Arg	Leu
				50					55					60
Gly	Lys	Asn	Leu	Tyr	Thr	Asn	Glu	Tyr	Val	Ala	Ile	Lys	Leu	Glu
				65					70					75
Pro	Ile	Lys	Ser	Arg	Ala	Leu	Gln	Leu	His	Leu	Glu	Tyr	Arg	Phe
				80					85					90
Tyr	Lys	Gln	Leu	Gly	Ser	Ala	Gly	Glu	Gly	Leu	Pro	Gln	Val	Tyr
				95					100					105
Tyr	Phe	Gly	Pro	Cys	Gly	Lys	Tyr	Asn	Ala	Met	Val	Leu	Glu	Leu
				110					115					120
Leu	Gly	Pro	Ser	Leu	Glu	Asp	Leu	Phe	Asp	Leu	Cys	Asp	Arg	Thr
				125					130					135
Phe	Thr	Leu	Lys	Thr	Val	Leu	Met	Ile	Ala	Ile	Gln	Leu	Leu	Ser
				140					145					150
Arg	Met	Glu	Tyr	Val	His	Ser	Lys	Asn	Leu	Ile	Tyr	Arg	Asp	Val
				155					160					165
Lys	Pro	Glu	Asn	Phe	Leu	Ile	Gly	Arg	Gln	Gly	Asn	Lys	Lys	Glu
				170					175					180
His	Val	Ile	His	Ile	Ile	Asp	Phe	Gly	Leu	Ala	Lys	Glu	Tyr	Ile
				185					190					195
Asp	Pro	Glu	Thr	Lys	Lys	His	Ile	Pro	Tyr	Arg	Glu	His	Lys	Ser
				200					205					210
Leu	Thr	Gly	Thr	Ala	Arg	Tyr	Met	Ser	Ile	Asn	Thr	His	Leu	Gly
				215					220					225
Lys	Glu	Gln	Ser	Arg	Arg	Asp	Asp	Leu	Glu	Ala	Leu	Gly	His	Met
				230					235					240
Phe	Met	Tyr	Phe	Leu	Arg	Gly	Ser	Leu	Pro	Trp	Gln	Gly	Leu	Lys
				245					250					255
Ala	Asp	Thr	Leu	Lys	Glu	Arg	Tyr	Gln	Lys	Ile	Gly	Asp	Thr	Lys
				260					265					270
Arg	Asn	Thr	Pro	Ile	Glu	Ala	Leu	Cys	Glu	Asn	Phe	Pro	Glu	Glu
				275					280					285
Met	Ala	Thr	Tyr	Leu	Arg	Tyr	Val	Arg	Arg	Leu	Asp	Phe	Phe	Glu
				290					295					300
Lys	Pro	Asp	Tyr	Glu	Tyr	Leu	Arg	Thr	Leu	Phe	Thr	Asp	Leu	Phe
				305					310					315
Glu	Lys	Lys	Gly	Tyr	Thr	Phe	Asp	Tyr	Ala	Tyr	Asp	Trp	Val	Gly
				320					325					330
Arg	Pro	Ile	Pro	Thr	Pro	Val	Gly	Ser	Val	His	Val	Asp	Ser	Gly
				335					340					345
Ala	Ser	Ala	Ile	Thr	Arg	Glu	Ser	His	Thr	His	Arg	Asp	Arg	Pro
				350					355					360

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Ser Gln Gln Gln Pro Leu Arg Asn Gln Asn Val Ser Ser Glu Arg
365 370 375
Arg Gly Glu Trp Glu Ile Gln Pro Ser Arg Gln Thr Asn Thr Ser
380 385 390
Tyr Leu Thr Ser His Leu Ala Ala Asp Arg His Gly Gly Ser Val
395 400 405
Gln Val Val Ser Ser Thr Asn Gly Glu Leu Asn Val Asp Asp Pro
410 415 420
Thr Gly Ala His Ser Asn Ala Pro Ile Thr Ala His Ala Glu Val
425 430 435
Glu Val Val Glu Glu Ala Lys Cys Cys Cys Phe Phe Lys Arg Lys
440 445 450
Arg Lys Lys Thr Ala Gln Arg His Lys
455

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&lt;210&gt; 16

&lt;211&gt; 1360

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 55064363CD1

&lt;400&gt; 16

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Met Lys Trp Val Gly Asp Thr Gly Val Gly Gly Asn Ile Pro Pro
1 5 10 15
Ser Phe Thr Thr Pro Gly Leu Ser Ser Arg Pro Gly Ala Met Val
20 25 30
Ala Asp Arg Ser Arg Trp Pro Leu Ala Gln Gly Lys Gly Ala Gln
35 40 45
Ala Gly Thr Trp Arg Ala Ala Val Glu Cys Ser Gly Arg Gly Leu
50 55 60
Gly Ala Ala Ser Glu Ser Pro Gln Cys Pro Pro Pro Pro Gly Val
65 70 75
Glu Gly Ala Ala Gly Pro Ala Glu Pro Asp Gly Ala Ala Glu Gly
80 85 90
Ala Ala Gly Gly Ser Gly Glu Gly Glu Ser Gly Gly Gly Pro Arg
95 100 105
Arg Ala Leu Arg Ala Val Tyr Val Arg Ser Glu Ser Ser Gln Gly
110 115 120
Gly Ala Ala Gly Gly Pro Glu Ala Gly Ala Arg Gln Cys Leu Leu
125 130 135
Arg Ala Cys Glu Ala Glu Gly Ala His Leu Thr Ser Val Pro Phe
140 145 150
Gly Glu Leu Asp Phe Gly Glu Thr Ala Val Leu Asp Ala Phe Tyr
155 160 165
Asp Ala Asp Val Ala Val Val Asp Met Ser Asp Val Ser Arg Gln
170 175 180
Pro Ser Leu Phe Tyr His Leu Gly Val Arg Glu Ser Phe Asp Met
185 190 195
Ala Asn Asn Val Ile Leu Tyr His Asp Thr Asp Ala Asp Thr Ala
200 205 210
Leu Ser Leu Lys Asp Met Val Thr Gln Lys Asn Thr Ala Ser Ser
215 220 225
Gly Asn Tyr Tyr Phe Ile Pro Tyr Ile Val Thr Pro Cys Thr Asp
230 235 240
Tyr Phe Cys Cys Glu Ser Asp Ala Gln Arg Arg Ala Ser Glu Tyr
245 250 255
Met Gln Pro Asn Trp Asp Asn Ile Leu Gly Pro Leu Cys Met Pro
260 265 270
Leu Val Asp Arg Phe Ile Ser Leu Leu Lys Asp Ile His Val Thr
275 280 285

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Ser Cys Val Tyr	Tyr Lys Glu Thr Leu	Leu Asn Asp Ile Arg	Lys
	290	295	300
Ala Arg Glu Lys	Tyr Gln Gly Glu Glu	Leu Ala Lys Glu Leu	Ala
	305	310	315
Arg Ile Lys Leu	Arg Met Asp Asn Thr	Glu Val Leu Thr Ser	Asp
	320	325	330
Ile Ile Ile Asn	Leu Leu Leu Ser Tyr	Arg Asp Ile Gln Asp	Tyr
	335	340	345
Asp Ala Met Val	Lys Leu Val Glu Thr	Leu Glu Met Leu Pro	Thr
	350	355	360
Cys Asp Leu Ala	Asp Gln His Asn Ile	Lys Phe His Tyr Ala	Phe
	365	370	375
Ala Leu Asn Arg	Arg Asn Ser Thr Gly	Asp Arg Glu Lys Ala	Leu
	380	385	390
Gln Ile Met Leu	Gln Val Leu Gln Ser	Cys Asp His Pro Gly	Pro
	395	400	405
Asp Met Phe Cys	Leu Cys Gly Arg Ile	Tyr Lys Asp Ile Phe	Leu
	410	415	420
Asp Ser Asp Cys	Lys Asp Asp Thr Ser	Arg Asp Ser Ala Ile	Glu
	425	430	435
Trp Tyr Arg Lys	Gly Phe Glu Leu Gln	Ser Ser Leu Tyr Ser	Gly
	440	445	450
Ile Asn Leu Ala	Val Leu Leu Ile Val	Ala Gly Gln Gln Phe	Glu
	455	460	465
Thr Ser Leu Glu	Leu Arg Lys Ile Gly	Val Arg Leu Asn Ser	Leu
	470	475	480
Leu Gly Arg Lys	Gly Ser Leu Glu Lys	Met Asn Asn Tyr Trp	Asp
	485	490	495
Val Gly Gln Phe	Phe Ser Val Ser Met	Leu Ala His Asp Val	Gly
	500	505	510
Lys Ala Val Gln	Ala Ala Glu Arg Leu	Phe Lys Leu Lys Pro	Pro
	515	520	525
Val Trp Tyr Leu	Arg Ser Leu Val Gln	Asn Leu Leu Leu Ile	Arg
	530	535	540
Arg Phe Lys Lys	Thr Ile Ile Glu His	Ser Pro Arg Gln Glu	Arg
	545	550	555
Leu Asn Phe Trp	Leu Asp Ile Ile Phe	Glu Ala Thr Asn Glu	Val
	560	565	570
Thr Asn Gly Leu	Arg Phe Pro Val Leu	Val Ile Glu Pro Thr	Lys
	575	580	585
Val Tyr Gln Pro	Ser Tyr Val Ser Ile	Asn Asn Glu Ala Glu	Glu
	590	595	600
Arg Thr Val Ser	Leu Trp His Val Ser	Pro Thr Glu Met Lys	Gln
	605	610	615
Met His Glu Trp	Asn Phe Thr Ala Ser	Ser Ile Lys Gly Ile	Ser
	620	625	630
Leu Ser Lys Phe	Asp Glu Arg Cys Cys	Phe Leu Tyr Val His	Asp
	635	640	645
Asn Ser Asp Asp	Phe Gln Ile Tyr Phe	Ser Thr Glu Glu Gln	Cys
	650	655	660
Ser Arg Phe Phe	Ser Leu Val Lys Glu	Met Ile Thr Asn Thr	Ala
	665	670	675
Gly Ser Thr Val	Glu Leu Glu Gly Glu	Thr Asp Gly Asp Thr	Leu
	680	685	690
Glu Tyr Glu Tyr	Asp His Asp Ala Asn	Gly Glu Arg Val Val	Leu
	695	700	705
Gly Lys Gly Thr	Tyr Gly Ile Val Tyr	Ala Gly Arg Asp Leu	Ser
	710	715	720
Asn Gln Val Arg	Ile Ala Ile Lys Glu	Ile Pro Glu Arg Asp	Ser
	725	730	735
Arg Tyr Ser Gln	Pro Leu His Glu Glu	Ile Ala Leu His Lys	Tyr
	740	745	750
Leu Lys His Arg	Asn Ile Val Gln Tyr	Leu Gly Ser Val Ser	Glu

755	760	765
Asn Gly Tyr Ile Lys Ile Phe Met Glu Gln Val Pro Gly Gly Ser		
770	775	780
Leu Ser Ala Leu Leu Arg Ser Lys Trp Gly Pro Met Lys Glu Pro		
785	790	795
Thr Ile Lys Phe Tyr Thr Lys Gln Ile Leu Glu Gly Leu Lys Tyr		
800	805	810
Leu His Glu Asn Gln Ile Val His Arg Asp Ile Lys Gly Asp Asn		
815	820	825
Val Leu Val Asn Thr Tyr Ser Gly Val Val Lys Ile Ser Asp Phe		
830	835	840
Gly Thr Ser Lys Arg Leu Ala Gly Val Asn Pro Cys Thr Glu Thr		
845	850	855
Phe Thr Gly Thr Leu Gln Tyr Met Ala Pro Glu Ile Ile Asp Gln		
860	865	870
Gly Pro Arg Gly Tyr Gly Ala Pro Ala Asp Ile Trp Ser Leu Gly		
875	880	885
Cys Thr Ile Ile Glu Met Ala Thr Ser Lys Pro Pro Phe His Glu		
890	895	900
Leu Gly Glu Pro Gln Ala Ala Met Phe Lys Val Gly Met Phe Lys		
905	910	915
Ile His Pro Glu Ile Pro Glu Ala Leu Ser Ala Glu Ala Arg Ala		
920	925	930
Phe Ile Leu Ser Cys Phe Glu Pro Asp Pro His Lys Arg Ala Thr		
935	940	945
Thr Ala Glu Leu Leu Arg Glu Gly Phe Leu Arg Gln Val Asn Lys		
950	955	960
Gly Lys Lys Asn Arg Ile Ala Phe Lys Pro Ser Glu Gly Pro Arg		
965	970	975
Gly Val Val Leu Ala Leu Pro Thr Gln Gly Glu Pro Met Ala Thr		
980	985	990
Ser Ser Ser Glu His Gly Ser Val Ser Pro Asp Ser Asp Ala Gln		
995	1000	1005
Pro Asp Ala Leu Phe Glu Arg Thr Arg Ala Pro Arg His His Leu		
1010	1015	1020
Gly His Leu Leu Ser Val Pro Asp Glu Ser Ser Ala Leu Glu Asp		
1025	1030	1035
Arg Gly Leu Ala Ser Ser Pro Glu Asp Arg Asp Gln Gly Leu Phe		
1040	1045	1050
Leu Leu Arg Lys Asp Ser Glu Arg Arg Ala Ile Leu Tyr Lys Ile		
1055	1060	1065
Leu Trp Glu Glu Gln Asn Gln Val Ala Ser Asn Leu Gln Glu Cys		
1070	1075	1080
Val Ala Gln Ser Ser Glu Glu Leu His Leu Ser Val Gly His Ile		
1085	1090	1095
Lys Gln Ile Ile Gly Ile Leu Arg Asp Phe Ile Arg Ser Pro Glu		
1100	1105	1110
His Arg Val Met Ala Thr Thr Ile Ser Lys Leu Lys Val Asp Leu		
1115	1120	1125
Asp Phe Asp Ser Ser Ser Ile Ser Gln Ile His Leu Val Leu Phe		
1130	1135	1140
Gly Phe Gln Asp Ala Val Asn Lys Ile Leu Arg Asn His Leu Ile		
1145	1150	1155
Arg Pro His Trp Met Phe Ala Met Asp Asn Ile Ile Arg Arg Ala		
1160	1165	1170
Val Gln Ala Ala Val Thr Ile Leu Ile Pro Glu Leu Arg Ala His		
1175	1180	1185
Phe Glu Pro Thr Cys Glu Thr Glu Gly Val Asp Lys Asp Met Asp		
1190	1195	1200
Glu Ala Glu Glu Gly Tyr Pro Pro Ala Thr Gly Pro Gly Gln Glu		
1205	1210	1215
Ala Gln Pro His Gln Gln His Leu Ser Leu Gln Leu Gly Glu Leu		
1220	1225	1230

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<210> 17
<211> 1345
<212> PRT
<213> Homo sapiens
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<400> 17

31/67

Cys	Ile	Val	Leu	Val	Thr	Glu	Leu	Met	Thr	Ser	Gly	Thr	Leu	Lys
				260					265					270
Thr	Tyr	Leu	Lys	Arg	Phe	Lys	Val	Met	Lys	Pro	Lys	Val	Leu	Arg
				275					280					285
Ser	Trp	Cys	Arg	Gln	Ile	Leu	Lys	Gly	Leu	Leu	Phe	Leu	His	Thr
				290					295					300
Arg	Thr	Pro	Pro	Ile	Ile	His	Arg	Asp	Leu	Lys	Cys	Asp	Asn	Ile
				305					310					315
Phe	Ile	Thr	Gly	Pro	Thr	Gly	Ser	Val	Lys	Ile	Gly	Asp	Leu	Gly
				320					325					330
Leu	Ala	Thr	Leu	Lys	Arg	Ala	Ser	Phe	Ala	Lys	Ser	Val	Ile	Gly
				335					340					345
Thr	Pro	Glu	Phe	Met	Ala	Pro	Glu	Met	Tyr	Glu	Glu	His	Tyr	Asp
				350					355					360
Glu	Ser	Val	Asp	Val	Tyr	Ala	Phe	Gly	Met	Cys	Met	Leu	Glu	Met
				365					370					375
Ala	Thr	Ser	Glu	Tyr	Pro	Tyr	Ser	Glu	Cys	Gln	Asn	Ala	Ala	Gln
				380					385					390
Ile	Tyr	Arg	Lys	Val	Thr	Cys	Gly	Ile	Lys	Pro	Ala	Ser	Phe	Glu
				395					400					405
Lys	Val	His	Asp	Pro	Glu	Ile	Lys	Glu	Ile	Ile	Gly	Glu	Cys	Ile
				410					415					420
Cys	Lys	Asn	Lys	Glu	Glu	Arg	Tyr	Glu	Ile	Lys	Asp	Leu	Leu	Ser
				425					430					435
His	Ala	Phe	Phe	Ala	Glu	Asp	Thr	Gly	Val	Arg	Val	Glu	Leu	Ala
				440					445					450
Glu	Glu	Asp	His	Gly	Arg	Lys	Ser	Thr	Ile	Ala	Leu	Arg	Leu	Trp
				455					460					465
Val	Glu	Asp	Pro	Lys	Lys	Leu	Lys	Gly	Lys	Pro	Lys	Asp	Asn	Gly
				470					475					480
Ala	Ile	Glu	Phe	Thr	Phe	Asp	Leu	Glu	Lys	Glu	Thr	Pro	Asp	Glu
				485					490					495
Val	Ala	Gln	Glu	Met	Ile	Glu	Ser	Gly	Phe	Phe	His	Glu	Ser	Asp
				500					505					510
Val	Lys	Ile	Val	Ala	Lys	Ser	Ile	Arg	Asp	Arg	Val	Ala	Leu	Ile
				515					520					525
Gln	Trp	Arg	Arg	Glu	Arg	Ile	Trp	Pro	Ala	Leu	Gln	Pro	Lys	Glu
				530					535					540
Gln	Gln	Asp	Val	Gly	Ser	Pro	Asp	Lys	Ala	Arg	Gly	Pro	Pro	Val
				545					550					555
Pro	Leu	Gln	Val	Gln	Val	Thr	Tyr	His	Ala	Gln	Ala	Gly	Gln	Pro
				560					565					570
Gly	Pro	Pro	Glu	Pro	Glu	Glu	Pro	Glu	Ala	Asp	Gln	His	Leu	Leu
				575					580					585
Pro	Pro	Thr	Leu	Pro	Thr	Ser	Ala	Thr	Ser	Leu	Ala	Ser	Asp	Ser
				590					595					600
Thr	Phe	Asp	Ser	Gly	Gln	Gly	Ser	Thr	Val	Tyr	Ser	Asp	Ser	Gln
				605					610					615
Ser	Ser	Gln	Gln	Ser	Val	Met	Leu	Gly	Ser	Leu	Ala	Asp	Ala	Ala
				620					625					630
Pro	Ser	Pro	Ala	Gln	Cys	Val	Cys	Ser	Pro	Pro	Val	Ser	Glu	Gly
				635					640					645
Pro	Val	Leu	Pro	Gln	Ser	Leu	Pro	Ser	Leu	Gly	Ala	Tyr	Gln	Gln
				650					655					660
Pro	Thr	Ala	Ala	Pro	Gly	Leu	Pro	Val	Gly	Ser	Val	Pro	Ala	Pro
				665					670					675
Ala	Cys	Pro	Pro	Ser	Leu	Gln	Gln	His	Phe	Pro	Asp	Pro	Ala	Met
				680					685					690
Ser	Phe	Ala	Pro	Val	Leu	Pro	Pro	Pro	Ser	Thr	Pro	Met	Pro	Thr
				695					700					705
Gly	Pro	Gly	Gln	Pro	Ala	Pro	Pro	Gly	Gln	Gln	Pro	Pro	Pro	Leu
				710					715					720
Ala	Gln	Pro	Thr	Pro	Leu	Pro	Gln	Val	Leu	Ala	Pro	Gln	Pro	Val

Val Pro Leu Gln	725	Val Pro Pro His	730	Leu Pro Pro Tyr	735
Pro Ala Ser Gln	740	Val Gly Ala Pro	745	Leu Lys Pro Leu	750
Met Pro Gln Ala	755	Pro Leu Gln Pro	760	Ala Gln Val Pro	765
Met Pro Pro Ile	770	Pro Val Val Pro	775	Ile Thr Pro Leu	780
Ile Asp Gly Leu	785	Pro Pro Ala Leu	790	Pro Thr Ala Thr	795
Val Pro Pro Met	800	Pro Pro Gln Tyr	805	Phe Ser Pro Ala	810
Leu Pro Ser Leu	815	Ala Ala Pro Leu	820	Pro Ala Ser Pro	825
Pro Leu Gln Ala	830	Val Lys Leu Pro	835	Pro Gly Ala Pro	840
Ala Met Pro Cys	845	Arg Thr Ile Val	850	Pro Ala Thr Ile	855
Pro Leu Leu Ala	860	Val Ala Pro Pro	865	Gly Val Ala Ala	870
His Ser Ala Val	875	Ala Gln Leu Pro	880	Gln Pro Val Tyr	885
Ala Phe Pro Gln	890	Met Ala Pro Thr	895	Val Pro Pro Ser	900
His Thr Val Gln	905	Asn Met Arg Ala	910	Pro Pro Gln Pro	915
Pro Pro Gln Pro	920	Thr Leu Pro Pro	925	Pro Val Leu Pro	930
Pro Thr Leu Pro	935	Pro Gln Pro Val	940	Pro Gln Pro Thr	945
Pro Pro Gln Pro	950	Val Leu Pro Pro	955	Met Leu Pro Pro	960
Pro Val Leu Pro	965	Pro Gln Pro Ala	970	Pro Val Arg Pro	975
Leu Gln Pro His	980	Leu Pro Glu Gln	985	Ala Pro Ala Ala	990
Gly Ser Gln Ile	995	Leu Gly His Pro	1000	Pro Tyr Ala Val	1005
Val Ala Ala Gln	1010	Val Pro Thr Val	1015	Pro Pro Ala Ala	1020
Leu Ser Pro Pro	1025	Leu Pro Glu Val	1030	Leu Leu Pro Ala	1035
Leu Leu Pro Gln	1040	Phe Pro Ser Ser	1045	Leu Ala Thr Val	1050
Val Gln Ser Val	1055	Pro Thr Gln Thr	1060	Ala Thr Leu Leu	1065
Asn Pro Pro Leu	1070	Pro Gly Gly Pro	1075	Gly Ile Ala Ser	1080
Thr Val Gln Leu	1085	Thr Val Glu Pro	1090	Glu Glu Gln Ala	1095
Gln Asp Lys Pro	1100	Pro Gly Leu Pro	1105	Cys Glu Ser Tyr	1110
Gly Ser Asp Val	1115	Thr Ser Gly Lys	1120	Glu Leu Ser Asp	1125
Gly Ala Phe Gly	1130	Gly Gly Arg Leu	1135	Glu Gly Arg Ala	1140
His His Arg Arg	1145	Ser Thr Arg Ala	1150	Arg Gln Glu Arg	1155
Ser Arg Pro Arg	1160	Leu Thr Ile Leu	1165	Asn Val Cys Asn	1170
Lys Met Val Glu	1175	Cys Thr Ile Leu	1180	Asn Thr Gly Asp	1185
	1190	Gln Leu Glu Thr	1195	His Asn His Lys	1200

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Thr Phe Lys Phe Asp Leu Asp Gly Asp Ala Pro Asp Glu Ile Ala
    1205                      1210                      1215
Thr Tyr Met Val Glu His Asp Phe Ile Leu Gln Ala Glu Arg Glu
    1220                      1225                      1230
Thr Phe Ile Glu Gln Met Lys Asp Val Met Asp Lys Ala Glu Asp
    1235                      1240                      1245
Met Leu Ser Glu Asp Thr Asp Ala Asp Arg Gly Ser Asp Pro Gly
    1250                      1255                      1260
Thr Ser Pro Pro His Leu Ser Thr Cys Gly Leu Gly Thr Gly Glu
    1265                      1270                      1275
Glu Ser Arg Gln Ser Gln Ala Asn Ala Pro Val Tyr Gln Gln Asn
    1280                      1285                      1290
Val Leu His Thr Gly Lys Arg Trp Phe Ile Ile Cys Pro Val Ala
    1295                      1300                      1305
Glu His Pro Ala Pro Glu Ala Pro Glu Ser Ser Pro Pro Leu Pro
    1310                      1315                      1320
Leu Ser Ser Leu Pro Cys Pro Ala Leu Phe Arg Met Ser Cys Ala
    1325                      1330                      1335
Ser Val Leu Ala Cys Pro Leu Ser Ala Cys
    1340                      1345

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&lt;210&gt; 18

&lt;211&gt; 2038

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 7476595CD1

&lt;400&gt; 18

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Met Thr Ala Glu Thr Pro Glu Thr Asp Glu Ser Val Ser Ser Ser
  1          5          10          15
Asn Ala Ser Leu Lys Leu Arg Arg Lys Pro Arg Glu Ser Asp Phe
    20          25          30
Glu Thr Ile Lys Leu Ile Ser Asn Gly Ala Tyr Gly Ala Val Tyr
    35          40          45
Phe Val Arg His Lys Glu Ser Arg Gln Arg Phe Ala Met Lys Lys
    50          55          60
Ile Asn Lys Gln Asn Leu Ile Leu Arg Asn Gln Ile Gln Gln Ala
    65          70          75
Phe Val Glu Arg Asp Ile Leu Thr Phe Ala Glu Asn Pro Phe Val
    80          85          90
Val Ser Met Tyr Cys Ser Phe Glu Thr Arg Arg His Leu Cys Met
    95          100          105
Val Met Glu Tyr Val Glu Gly Gly Asp Cys Ala Thr Leu Met Lys
    110          115          120
Asn Met Gly Pro Leu Pro Val Asp Met Ala Arg Met Tyr Phe Ala
    125          130          135
Glu Thr Val Leu Ala Leu Glu Tyr Leu His Asn Tyr Gly Ile Val
    140          145          150
His Arg Asp Leu Lys Pro Asp Asn Leu Leu Val Thr Ser Met Gly
    155          160          165
His Ile Lys Leu Thr Asp Phe Gly Leu Ser Lys Val Gly Leu Met
    170          175          180
Ser Met Thr Thr Asn Leu Tyr Glu Gly His Ile Glu Lys Asp Ala
    185          190          195
Arg Glu Phe Leu Asp Lys Gln Val Cys Gly Thr Pro Glu Tyr Ile
    200          205          210
Ala Pro Glu Val Ile Leu Arg Gln Gly Tyr Gly Lys Pro Val Asp
    215          220          225
Trp Trp Ala Met Gly Ile Ile Leu Tyr Glu Phe Leu Val Gly Cys
    230          235          240

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Val	Pro	Phe	Phe	Gly	Asp	Thr	Pro	Glu	Glu	Leu	Phe	Gly	Gln	Val
				245					250					255
Ile	Ser	Asp	Glu	Ile	Asn	Trp	Pro	Glu	Lys	Asp	Glu	Ala	Pro	Pro
				260					265					270
Pro	Asp	Ala	Gln	Asp	Leu	Ile	Thr	Leu	Leu	Leu	Arg	Gln	Asn	Pro
				275					280					285
Leu	Glu	Arg	Leu	Gly	Thr	Gly	Gly	Ala	Tyr	Glu	Val	Lys	Gln	His
				290					295					300
Arg	Phe	Phe	Arg	Ser	Leu	Asp	Trp	Asn	Ser	Leu	Leu	Arg	Gln	Lys
				305					310					315
Ala	Glu	Phe	Ile	Pro	Gln	Leu	Glu	Ser	Glu	Asp	Asp	Thr	Ser	Tyr
				320					325					330
Phe	Asp	Thr	Arg	Ser	Glu	Lys	Tyr	His	His	Met	Glu	Thr	Glu	Glu
				335					340					345
Glu	Asp	Asp	Thr	Asn	Asp	Glu	Asp	Phe	Asn	Val	Glu	Ile	Arg	Gln
				350					355					360
Phe	Ser	Ser	Cys	Ser	His	Arg	Phe	Ser	Lys	Leu	Phe	Leu	Asn	Asp
				365					370					375
Tyr	Leu	Asp	Ala	Pro	Ala	Asn	Gly	Pro	Ala	Leu	Pro	Ser	Cys	Val
				380					385					390
Trp	Glu	Trp	His	Arg	Gly	Lys	Asp	Phe	Pro	Gly	Glu	Gly	Gly	Ser
				395					400					405
Gln	Ser	Val	Leu	Glu	Pro	Gly	Gln	Lys	Leu	Ala	Lys	Cys	Gly	Leu
				410					415					420
Arg	Pro	Gly	Leu	Phe	Ser	Gly	Pro	Ser	Lys	Thr	Thr	Met	Pro	Thr
				425					430					435
Pro	Lys	His	Cys	Phe	Leu	Leu	Cys	Leu	Asp	Thr	Glu	Ser	Asn	Arg
				440					445					450
His	Lys	Leu	Ser	Ser	Gly	Leu	Leu	Pro	Lys	Leu	Ala	Ile	Ser	Thr
				455					460					465
Glu	Gly	Glu	Gln	Asp	Glu	Ala	Ala	Ser	Cys	Pro	Gly	Asp	Pro	His
				470					475					480
Glu	Glu	Pro	Gly	Lys	Pro	Ala	Leu	Pro	Pro	Glu	Glu	Cys	Ala	Gln
				485					490					495
Glu	Glu	Pro	Glu	Val	Thr	Thr	Pro	Ala	Ser	Thr	Ile	Ser	Ser	Ser
				500					505					510
Thr	Leu	Ser	Asp	Met	Phe	Ala	Val	Ser	Pro	Leu	Gly	Ser	Pro	Met
				515					520					525
Ser	Pro	His	Ser	Leu	Ser	Ser	Asp	Pro	Ser	Ser	Ser	Arg	Asp	Ser
				530					535					540
Ser	Pro	Ser	Arg	Asp	Ser	Ser	Ala	Ala	Ser	Ala	Ser	Pro	His	Gln
				545					550					555
Pro	Ile	Val	Ile	His	Ser	Ser	Gly	Lys	Asn	Tyr	Gly	Phe	Thr	Ile
				560					565					570
Arg	Ala	Ile	Arg	Val	Tyr	Val	Gly	Asp	Ser	Asp	Ile	Tyr	Thr	Val
				575					580					585
His	His	Ile	Val	Trp	Asn	Val	Glu	Glu	Gly	Ser	Pro	Ala	Cys	Gln
				590					595					600
Ala	Gly	Leu	Lys	Ala	Gly	Asp	Leu	Ile	Thr	His	Ile	Asn	Gly	Glu
				605					610					615
Pro	Val	His	Gly	Leu	Val	His	Thr	Glu	Val	Ile	Glu	Leu	Leu	Leu
				620					625					630
Lys	Ser	Gly	Asn	Lys	Val	Ser	Ile	Thr	Thr	Thr	Pro	Phe	Glu	Asn
				635					640					645
Thr	Ser	Ile	Lys	Thr	Gly	Pro	Ala	Arg	Arg	Asn	Ser	Tyr	Lys	Ser
				650					655					660
Arg	Met	Val	Arg	Arg	Ser	Lys	Lys	Ser	Lys	Lys	Lys	Glu	Ser	Leu
				665					670					675
Glu	Arg	Arg	Arg	Ser	Leu	Phe	Lys	Lys	Leu	Ala	Lys	Gln	Pro	Ser
				680					685					690
Pro	Leu	Leu	His	Thr	Ser	Arg	Ser	Phe	Ser	Cys	Leu	Asn	Arg	Ser
				695					700					705
Leu	Ser	Ser	Gly	Glu	Ser	Leu	Pro	Gly	Ser	Pro	Thr	His	Ser	Leu

	710		715		720
Ser Pro Arg Ser	Pro Thr Pro Ser Tyr Arg	Ser Thr Pro Asp Phe			
	725		730		735
Pro Ser Gly Thr	Asn Ser Ser Gln Ser Ser Ser Pro Ser Ser				
	740		745		750
Ala Pro Asn Ser	Pro Ala Gly Ser Gly His Ile Arg Pro Ser Thr				
	755		760		765
Leu His Gly Leu	Ala Pro Lys Leu Gly Gly Gln Arg Tyr Arg Ser				
	770		775		780
Gly Arg Arg Lys	Ser Ala Gly Asn Ile Pro Leu Ser Pro Leu Ala				
	785		790		795
Arg Thr Pro Ser	Pro Thr Pro Gln Pro Thr Ser Pro Gln Arg Ser				
	800		805		810
Pro Ser Pro Leu	Leu Gly His Ser Leu Gly Asn Ser Lys Ile Ala				
	815		820		825
Gln Ala Phe Pro	Ser Lys Met His Ser Pro Pro Thr Ile Val Arg				
	830		835		840
His Ile Val Arg	Pro Lys Ser Ala Glu Pro Pro Arg Ser Pro Leu				
	845		850		855
Leu Lys Arg Val	Gln Ser Glu Glu Lys Leu Ser Pro Ser Tyr Gly				
	860		865		870
Ser Asp Lys Lys	His Leu Cys Ser Arg Lys His Ser Leu Glu Val				
	875		880		885
Thr Gln Glu Glu	Val Gln Arg Glu Gln Ser Gln Arg Glu Ala Pro				
	890		895		900
Leu Gln Ser Leu	Asp Glu Asn Val Cys Asp Val Pro Pro Leu Ser				
	905		910		915
Arg Ala Arg Pro	Val Glu Gln Gly Cys Leu Lys Arg Pro Val Ser				
	920		925		930
Arg Lys Val Gly	Arg Gln Glu Ser Val Asp Asp Leu Asp Arg Asp				
	935		940		945
Lys Leu Lys Ala	Lys Val Val Val Lys Lys Ala Asp Gly Phe Pro				
	950		955		960
Glu Lys Gln Glu	Ser His Gln Lys Ser His Gly Pro Gly Ser Asp				
	965		970		975
Leu Glu Asn Phe	Ala Leu Phe Lys Leu Glu Glu Arg Glu Lys Lys				
	980		985		990
Val Tyr Pro Lys	Ala Val Glu Arg Ser Ser Thr Phe Glu Asn Lys				
	995		1000		1005
Ala Ser Met Gln	Glu Ala Pro Pro Leu Gly Ser Leu Leu Lys Asp				
	1010		1015		1020
Ala Leu His Lys	Gln Ala Ser Val Arg Ala Ser Glu Gly Ala Met				
	1025		1030		1035
Ser Asp Gly Arg	Val Pro Ala Glu His Arg Gln Gly Gly Gly Asp				
	1040		1045		1050
Phe Arg Arg Ala	Pro Ala Pro Gly Thr Leu Gln Asp Gly Leu Cys				
	1055		1060		1065
His Ser Leu Asp	Arg Gly Ile Ser Gly Lys Gly Glu Gly Thr Glu				
	1070		1075		1080
Lys Ser Ser Gln	Ala Lys Glu Leu Leu Arg Cys Glu Lys Leu Asp				
	1085		1090		1095
Ser Lys Leu Ala	Asn Ile Asp Tyr Leu Arg Lys Lys Met Ser Leu				
	1100		1105		1110
Glu Asp Lys Glu	Asp Asn Leu Cys Pro Val Leu Lys Pro Lys Met				
	1115		1120		1125
Thr Ala Gly Ser	His Glu Cys Leu Pro Gly Asn Pro Val Arg Pro				
	1130		1135		1140
Thr Gly Gly Gln	Gln Glu Pro Pro Pro Ala Ser Glu Ser Arg Ala				
	1145		1150		1155
Phe Val Ser Ser	Thr His Ala Ala Gln Met Ser Ala Val Ser Phe				
	1160		1165		1170
Val Pro Leu Lys	Ala Leu Thr Gly Arg Val Asp Ser Gly Thr Glu				
	1175		1180		1185



Lys Pro Gly Leu Val	Ala Pro Glu Ser Pro	Val Arg Lys Ser Pro	1190	1195	1200
Ser Glu Tyr Lys Leu	Glu Gly Arg Ser Val	Ser Cys Leu Lys Pro	1205	1210	1215
Ile Glu Gly Thr Leu	Asp Ile Ala Leu Leu	Ser Gly Pro Gln Ala	1220	1225	1230
Ser Lys Thr Glu Leu	Pro Ser Pro Glu Ser	Ala Gln Ser Pro Ser	1235	1240	1245
Pro Ser Gly Asp Val	Arg Ala Ser Val Pro	Pro Val Leu Pro Ser	1250	1255	1260
Ser Ser Gly Lys Lys	Asn Asp Thr Thr Ser	Ala Arg Glu Leu Ser	1265	1270	1275
Pro Ser Ser Leu Lys	Met Asn Lys Ser Tyr	Leu Leu Glu Pro Trp	1280	1285	1290
Phe Leu Pro Pro Ser	Arg Gly Leu Gln Asn	Ser Pro Ala Val Ser	1295	1300	1305
Leu Pro Asp Pro Glu	Phe Lys Arg Asp Arg	Lys Gly Pro His Pro	1310	1315	1320
Thr Ala Arg Ser Pro	Gly Thr Val Met Glu	Ser Asn Pro Gln Gln	1325	1330	1335
Arg Glu Gly Ser Ser	Pro Lys His Gln Asp	His Thr Thr Asp Pro	1340	1345	1350
Lys Leu Leu Thr Cys	Leu Gly Gln Asn Leu	His Ser Pro Asp Leu	1355	1360	1365
Ala Arg Pro Arg Cys	Pro Leu Pro Pro Glu	Ala Ser Pro Ser Arg	1370	1375	1380
Glu Lys Pro Gly Leu	Arg Glu Ser Ser Glu	Arg Gly Pro Pro Thr	1385	1390	1395
Ala Arg Ser Glu Arg	Ser Ala Ala Arg Ala	Asp Thr Cys Arg Glu	1400	1405	1410
Pro Ser Met Glu Leu	Cys Phe Pro Glu Thr	Ala Lys Thr Ser Asp	1415	1420	1425
Asn Ser Lys Asn Leu	Leu Ser Val Gly Arg	Thr His Pro Asp Phe	1430	1435	1440
Tyr Thr Gln Thr Gln	Ala Met Glu Lys Ala	Trp Ala Pro Gly Gly	1445	1450	1455
Lys Thr Asn His Lys	Asp Gly Pro Gly Glu	Ala Arg Pro Pro Pro	1460	1465	1470
Arg Asp Asn Ser Ser	Leu His Ser Ala Gly	Ile Pro Cys Glu Lys	1475	1480	1485
Glu Leu Gly Lys Val	Arg Arg Gly Val Glu	Pro Lys Pro Glu Ala	1490	1495	1500
Leu Leu Ala Arg Arg	Ser Leu Gln Pro Pro	Gly Ile Glu Ser Glu	1505	1510	1515
Lys Ser Glu Lys Leu	Ser Ser Phe Pro Ser	Leu Gln Lys Asp Gly	1520	1525	1530
Ala Lys Glu Pro Glu	Arg Lys Glu Gln Pro	Leu Gln Arg His Pro	1535	1540	1545
Ser Ser Ile Pro Pro	Pro Pro Leu Thr Ala	Lys Asp Leu Ser Ser	1550	1555	1560
Pro Ala Ala Arg Gln	His Cys Ser Ser Pro	Ser His Ala Ser Gly	1565	1570	1575
Arg Glu Pro Gly Ala	Lys Pro Ser Thr Ala	Glu Pro Ser Ser Ser	1580	1585	1590
Pro Gln Asp Pro Pro	Lys Pro Val Ala Ala	His Ser Glu Ser Ser	1595	1600	1605
Ser His Lys Pro Arg	Pro Gly Pro Asp Pro	Gly Pro Pro Lys Thr	1610	1615	1620
Lys His Pro Asp Arg	Ser Leu Ser Ser Gln	Lys Pro Ser Val Gly	1625	1630	1635
Ala Thr Lys Gly Lys	Glu Pro Ala Thr Gln	Ser Leu Gly Gly Ser	1640	1645	1650
Ser Arg Glu Gly Lys	Gly His Ser Lys Ser	Gly Pro Asp Val Phe			

1655	1660	1665
Pro Ala Thr Pro Gly Ser Gln Asn Lys Ala Ser Asp Gly Ile Gly		
1670	1675	1680
Gln Gly Glu Gly Gly Pro Ser Val Pro Leu His Thr Asp Arg Ala		
1685	1690	1695
Pro Leu Asp Ala Lys Pro Gln Pro Thr Ser Gly Gly Arg Pro Leu		
1700	1705	1710
Glu Val Leu Glu Lys Pro Val His Leu Pro Arg Pro Gly His Pro		
1715	1720	1725
Gly Pro Ser Glu Pro Ala Asp Gln Lys Leu Ser Ala Val Gly Glu		
1730	1735	1740
Lys Gln Thr Leu Ser Pro Lys His Pro Lys Pro Ser Thr Val Lys		
1745	1750	1755
Asp Cys Pro Thr Leu Cys Lys Gln Thr Asp Asn Arg Gln Thr Asp		
1760	1765	1770
Lys Ser Pro Ser Gln Pro Ala Ala Asn Thr Asp Arg Arg Ala Glu		
1775	1780	1785
Gly Lys Lys Cys Thr Glu Ala Leu Tyr Ala Pro Ala Glu Gly Asp		
1790	1795	1800
Lys Leu Glu Ala Gly Leu Ser Phe Val His Ser Glu Asn Arg Leu		
1805	1810	1815
Lys Gly Ala Glu Arg Pro Ala Ala Gly Val Gly Lys Gly Phe Pro		
1820	1825	1830
Glu Ala Arg Gly Lys Gly Pro Gly Pro Gln Lys Pro Pro Thr Glu		
1835	1840	1845
Ala Asp Lys Pro Asn Gly Met Lys Arg Ser Pro Ser Ala Thr Gly		
1850	1855	1860
Gln Ser Ser Phe Arg Ser Thr Ala Leu Pro Glu Lys Ser Leu Ser		
1865	1870	1875
Cys Ser Ser Ser Phe Pro Glu Thr Arg Ala Gly Val Arg Glu Ala		
1880	1885	1890
Ser Ala Ala Ser Ser Asp Thr Ser Ser Ala Lys Ala Ala Gly Gly		
1895	1900	1905
Met Leu Glu Leu Pro Ala Pro Ser Asn Arg Asp His Arg Lys Ala		
1910	1915	1920
Gln Pro Ala Gly Glu Gly Arg Thr His Met Thr Lys Ser Asp Ser		
1925	1930	1935
Leu Pro Ser Phe Arg Val Ser Thr Leu Pro Leu Glu Ser His His		
1940	1945	1950
Pro Asp Pro Asn Thr Met Gly Gly Ala Ser His Arg Asp Arg Ala		
1955	1960	1965
Leu Ser Val Thr Ala Thr Val Gly Glu Thr Lys Gly Lys Asp Pro		
1970	1975	1980
Ala Pro Ala Gln Pro Pro Pro Ala Arg Lys Gln Asn Val Gly Arg		
1985	1990	1995
Asp Val Thr Lys Pro Ser Pro Ala Pro Asn Thr Asp Arg Pro Ile		
2000	2005	2010
Ser Leu Ser Asn Glu Lys Asp Phe Val Val Arg Gln Arg Arg Gly		
2015	2020	2025
Lys Glu Ser Leu Arg Ser Ser Pro His Lys Lys Ala Leu		
2030	2035	

&lt;210&gt; 19

&lt;211&gt; 1770

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 71824382CD1

&lt;400&gt; 19

Met Ser Gly Glu Val Arg Leu Arg Gln Leu Glu Gln Phe Ile Leu

1	5	10	15
Asp Gly Pro Ala Gln Thr Asn Gly Gln Cys Phe Ser Val Glu Thr			
	20	25	30
Leu Leu Asp Ile Leu Ile Cys Leu Tyr Asp Glu Cys Asn Asn Ser			
	35	40	45
Pro Leu Arg Arg Glu Lys Asn Ile Leu Glu Tyr Leu Glu Trp Ala			
	50	55	60
Lys Pro Phe Thr Ser Lys Val Lys Gln Met Arg Leu His Arg Glu			
	65	70	75
Asp Phe Glu Ile Leu Lys Val Ile Gly Arg Gly Ala Phe Gly Glu			
	80	85	90
Val Ala Val Val Lys Leu Lys Asn Ala Asp Lys Val Phe Ala Met			
	95	100	105
Lys Ile Leu Asn Lys Trp Glu Met Leu Lys Arg Ala Glu Thr Ala			
	110	115	120
Cys Phe Arg Glu Glu Arg Asp Val Leu Val Asn Gly Asp Asn Lys			
	125	130	135
Trp Ile Thr Thr Leu His Tyr Ala Phe Gln Asp Asp Asn Asn Leu			
	140	145	150
Tyr Leu Val Met Asp Tyr Tyr Val Gly Gly Asp Leu Leu Thr Leu			
	155	160	165
Leu Ser Lys Phe Glu Asp Arg Leu Pro Glu Asp Met Ala Arg Phe			
	170	175	180
Tyr Leu Ala Glu Met Val Ile Ala Ile Asp Ser Val His Gln Leu			
	185	190	195
His Tyr Val His Arg Asp Ile Lys Pro Asp Asn Ile Leu Met Asp			
	200	205	210
Met Asn Gly His Ile Arg Leu Ala Asp Phe Gly Ser Cys Leu Lys			
	215	220	225
Leu Met Glu Asp Gly Thr Val Gln Ser Ser Val Ala Val Gly Thr			
	230	235	240
Pro Asp Tyr Ile Ser Pro Glu Ile Leu Gln Ala Met Glu Asp Gly			
	245	250	255
Lys Gly Arg Tyr Gly Pro Glu Cys Asp Trp Trp Ser Leu Gly Val			
	260	265	270
Cys Met Tyr Glu Met Leu Tyr Gly Glu Thr Pro Phe Tyr Ala Glu			
	275	280	285
Ser Leu Val Glu Thr Tyr Gly Lys Ile Met Asn His Lys Glu Arg			
	290	295	300
Phe Gln Phe Pro Ala Gln Val Thr Asp Val Ser Glu Asn Ala Lys			
	305	310	315
Asp Leu Ile Arg Arg Leu Ile Cys Ser Arg Glu His Arg Leu Gly			
	320	325	330
Gln Asn Gly Ile Glu Asp Phe Lys Lys His Pro Phe Phe Ser Gly			
	335	340	345
Ile Asp Trp Asp Asn Ile Arg Asn Cys Glu Ala Pro Tyr Ile Pro			
	350	355	360
Glu Val Ser Ser Pro Thr Asp Thr Ser Asn Phe Asp Val Asp Asp			
	365	370	375
Asp Cys Leu Lys Asn Ser Glu Thr Met Pro Pro Pro Thr His Thr			
	380	385	390
Ala Phe Ser Gly His His Leu Pro Phe Val Gly Phe Thr Tyr Thr			
	395	400	405
Ser Ser Cys Val Leu Ser Asp Arg Ser Cys Leu Arg Val Thr Ala			
	410	415	420
Gly Pro Thr Ser Leu Asp Leu Asp Val Asn Val Gln Arg Thr Leu			
	425	430	435
Asp Asn Asn Leu Ala Thr Glu Ala Tyr Glu Arg Arg Ile Lys Arg			
	440	445	450
Leu Glu Gln Glu Lys Leu Glu Leu Ser Arg Lys Leu Gln Glu Ser			
	455	460	465
Thr Gln Thr Val Gln Ala Leu Gln Tyr Ser Thr Val Asp Gly Pro			
	470	475	480

Leu Thr Ala Ser	Lys Asp Leu Glu Ile	Lys Asn Leu Lys Glu Glu	485	490	495
Ile Glu Lys Leu	Arg Lys Gln Val Thr	Glu Ser Ser His Leu Glu	500	505	510
Gln Gln Leu Glu	Glu Ala Asn Ala Val	Arg Gln Glu Leu Asp Asp	515	520	525
Ala Phe Arg Gln	Ile Lys Ala Tyr Glu	Lys Gln Ile Lys Thr Leu	530	535	540
Gln Gln Glu Arg	Glu Asp Leu Asn Lys	Glu Leu Val Gln Ala Ser	545	550	555
Glu Arg Leu Lys	Asn Gln Ser Lys Glu	Leu Lys Asp Ala His Cys	560	565	570
Gln Arg Lys Leu	Ala Met Gln Glu Phe	Met Glu Ile Asn Glu Arg	575	580	585
Leu Thr Glu Leu	His Thr Gln Lys Gln	Lys Leu Ala Arg His Val	590	595	600
Arg Asp Lys Glu	Glu Glu Val Asp Leu	Val Met Gln Lys Val Glu	605	610	615
Ser Leu Arg Gln	Glu Leu Arg Arg Thr	Glu Arg Ala Lys Lys Glu	620	625	630
Leu Glu Val His	Thr Glu Ala Leu Ala	Ala Glu Ala Ser Lys Asp	635	640	645
Arg Lys Leu Arg	Glu Gln Ser Glu His	Tyr Ser Lys Gln Leu Glu	650	655	660
Asn Glu Leu Glu	Gly Leu Lys Gln Lys	Gln Ile Ser Tyr Ser Pro	665	670	675
Gly Val Cys Ser	Ile Glu His Gln Gln	Glu Ile Thr Lys Leu Lys	680	685	690
Thr Asp Leu Glu	Lys Lys Ser Ile Phe	Tyr Glu Glu Glu Leu Ser	695	700	705
Lys Arg Glu Gly	Ile His Ala Asn Glu	Ile Lys Asn Leu Lys Lys	710	715	720
Glu Leu His Asp	Ser Glu Gly Gln Gln	Leu Ala Leu Asn Lys Glu	725	730	735
Ile Met Ile Leu	Lys Asp Lys Leu Glu	Lys Thr Arg Arg Glu Ser	740	745	750
Gln Ser Glu Arg	Glu Glu Phe Glu Ser	Glu Phe Lys Gln Gln Tyr	755	760	765
Glu Arg Glu Lys	Val Leu Leu Thr Glu	Glu Asn Lys Lys Leu Thr	770	775	780
Ser Glu Leu Asp	Lys Leu Thr Thr Leu	Tyr Glu Asn Leu Ser Ile	785	790	795
His Asn Gln Gln	Leu Glu Glu Glu Val	Lys Asp Leu Ala Asp Lys	800	805	810
Lys Glu Ser Val	Ala His Trp Glu Ala	Gln Ile Thr Glu Ile Ile	815	820	825
Gln Trp Val Ser	Asp Glu Lys Asp Ala	Arg Gly Tyr Leu Gln Ala	830	835	840
Leu Ala Ser Lys	Met Thr Glu Glu Leu	Glu Ala Leu Arg Asn Ser	845	850	855
Ser Leu Gly Thr	Arg Ala Thr Asp Met	Pro Trp Lys Met Arg Arg	860	865	870
Phe Ala Lys Leu	Asp Met Ser Ala Arg	Leu Glu Leu Gln Ser Ala	875	880	885
Leu Asp Ala Glu	Ile Arg Ala Lys Gln	Ala Ile Gln Glu Glu Leu	890	895	900
Asn Lys Val Lys	Ala Ser Asn Ile Ile	Thr Glu Cys Lys Leu Lys	905	910	915
Asp Ser Glu Lys	Lys Asn Leu Glu Leu	Ser Glu Ile Glu Gln	920	925	930
Leu Ile Lys Asp	Thr Glu Glu Leu Arg	Ser Glu Lys Gly Ile Glu	935	940	945
His Gln Asp Ser	Gln His Ser Phe Leu	Ala Phe Leu Asn Thr Pro			

Thr Asp Ala Leu	950	Thr Asp Ala Leu	955	Thr Asp Ala Leu	960
Asp Gln Phe Glu Asp Ser Phe Ser Ser Ser Ser		Asp Gln Phe Glu Asp Ser Phe Ser Ser Ser Ser		Asp Gln Phe Glu Asp Ser Phe Ser Ser Ser Ser	
965		970		975	
Ser Ser Leu Ile Asp Phe Leu Asp Asp Thr Asp Pro Val Glu Asn		Ser Ser Leu Ile Asp Phe Leu Asp Asp Thr Asp Pro Val Glu Asn		Ser Ser Leu Ile Asp Phe Leu Asp Asp Thr Asp Pro Val Glu Asn	
980		985		990	
Thr Tyr Val Trp Asn Pro Ser Val Lys Phe His Ile Gln Ser Arg		Thr Tyr Val Trp Asn Pro Ser Val Lys Phe His Ile Gln Ser Arg		Thr Tyr Val Trp Asn Pro Ser Val Lys Phe His Ile Gln Ser Arg	
995		1000		1005	
Ser Thr Ser Pro Ser Thr Ser Ser Glu Ala Glu Pro Val Lys Thr		Ser Thr Ser Pro Ser Thr Ser Ser Glu Ala Glu Pro Val Lys Thr		Ser Thr Ser Pro Ser Thr Ser Ser Glu Ala Glu Pro Val Lys Thr	
1010		1015		1020	
Val Asp Ser Thr Pro Leu Ser Val His Thr Pro Thr Leu Arg Lys		Val Asp Ser Thr Pro Leu Ser Val His Thr Pro Thr Leu Arg Lys		Val Asp Ser Thr Pro Leu Ser Val His Thr Pro Thr Leu Arg Lys	
1025		1030		1035	
Lys Gly Cys Pro Gly Ser Thr Gly Phe Pro Pro Lys Arg Lys Thr		Lys Gly Cys Pro Gly Ser Thr Gly Phe Pro Pro Lys Arg Lys Thr		Lys Gly Cys Pro Gly Ser Thr Gly Phe Pro Pro Lys Arg Lys Thr	
1040		1045		1050	
His Gln Phe Phe Val Lys Ser Phe Thr Thr Pro Thr Lys Cys His		His Gln Phe Phe Val Lys Ser Phe Thr Thr Pro Thr Lys Cys His		His Gln Phe Phe Val Lys Ser Phe Thr Thr Pro Thr Lys Cys His	
1055		1060		1065	
Gln Cys Thr Ser Leu Met Val Gly Leu Ile Arg Gln Gly Cys Ser		Gln Cys Thr Ser Leu Met Val Gly Leu Ile Arg Gln Gly Cys Ser		Gln Cys Thr Ser Leu Met Val Gly Leu Ile Arg Gln Gly Cys Ser	
1070		1075		1080	
Cys Glu Val Cys Gly Phe Ser Cys His Ile Thr Cys Val Asn Lys		Cys Glu Val Cys Gly Phe Ser Cys His Ile Thr Cys Val Asn Lys		Cys Glu Val Cys Gly Phe Ser Cys His Ile Thr Cys Val Asn Lys	
1085		1090		1095	
Ala Pro Thr Thr Cys Pro Val Pro Pro Glu Gln Thr Lys Gly Pro		Ala Pro Thr Thr Cys Pro Val Pro Pro Glu Gln Thr Lys Gly Pro		Ala Pro Thr Thr Cys Pro Val Pro Pro Glu Gln Thr Lys Gly Pro	
1100		1105		1110	
Leu Gly Ile Asp Pro Gln Lys Gly Ile Gly Thr Ala Tyr Glu Gly		Leu Gly Ile Asp Pro Gln Lys Gly Ile Gly Thr Ala Tyr Glu Gly		Leu Gly Ile Asp Pro Gln Lys Gly Ile Gly Thr Ala Tyr Glu Gly	
1115		1120		1125	
His Val Arg Ile Pro Lys Pro Ala Gly Val Lys Lys Gly Trp Gln		His Val Arg Ile Pro Lys Pro Ala Gly Val Lys Lys Gly Trp Gln		His Val Arg Ile Pro Lys Pro Ala Gly Val Lys Lys Gly Trp Gln	
1130		1135		1140	
Arg Ala Leu Ala Ile Val Cys Asp Phe Lys Leu Phe Leu Tyr Asp		Arg Ala Leu Ala Ile Val Cys Asp Phe Lys Leu Phe Leu Tyr Asp		Arg Ala Leu Ala Ile Val Cys Asp Phe Lys Leu Phe Leu Tyr Asp	
1145		1150		1155	
Ile Ala Glu Gly Lys Ala Ser Gln Pro Ser Val Val Ile Ser Gln		Ile Ala Glu Gly Lys Ala Ser Gln Pro Ser Val Val Ile Ser Gln		Ile Ala Glu Gly Lys Ala Ser Gln Pro Ser Val Val Ile Ser Gln	
1160		1165		1170	
Val Ile Asp Met Arg Asp Glu Glu Phe Ser Val Ser Ser Val Leu		Val Ile Asp Met Arg Asp Glu Glu Phe Ser Val Ser Ser Val Leu		Val Ile Asp Met Arg Asp Glu Glu Phe Ser Val Ser Ser Val Leu	
1175		1180		1185	
Ala Ser Asp Val Ile His Ala Ser Arg Lys Asp Ile Pro Cys Ile		Ala Ser Asp Val Ile His Ala Ser Arg Lys Asp Ile Pro Cys Ile		Ala Ser Asp Val Ile His Ala Ser Arg Lys Asp Ile Pro Cys Ile	
1190		1195		1200	
Phe Arg Val Thr Ala Ser Gln Leu Ser Ala Ser Asn Asn Lys Cys		Phe Arg Val Thr Ala Ser Gln Leu Ser Ala Ser Asn Asn Lys Cys		Phe Arg Val Thr Ala Ser Gln Leu Ser Ala Ser Asn Asn Lys Cys	
1205		1210		1215	
Ser Ile Leu Met Leu Ala Asp Thr Glu Asn Glu Lys Asn Lys Trp		Ser Ile Leu Met Leu Ala Asp Thr Glu Asn Glu Lys Asn Lys Trp		Ser Ile Leu Met Leu Ala Asp Thr Glu Asn Glu Lys Asn Lys Trp	
1220		1225		1230	
Val Gly Val Leu Ser Glu Leu His Lys Ile Leu Lys Lys Asn Lys		Val Gly Val Leu Ser Glu Leu His Lys Ile Leu Lys Lys Asn Lys		Val Gly Val Leu Ser Glu Leu His Lys Ile Leu Lys Lys Asn Lys	
1235		1240		1245	
Phe Arg Asp Arg Ser Val Tyr Val Pro Lys Glu Ala Tyr Asp Ser		Phe Arg Asp Arg Ser Val Tyr Val Pro Lys Glu Ala Tyr Asp Ser		Phe Arg Asp Arg Ser Val Tyr Val Pro Lys Glu Ala Tyr Asp Ser	
1250		1255		1260	
Thr Leu Pro Leu Ile Lys Thr Thr Gln Ala Ala Ala Ile Ile Asp		Thr Leu Pro Leu Ile Lys Thr Thr Gln Ala Ala Ala Ile Ile Asp		Thr Leu Pro Leu Ile Lys Thr Thr Gln Ala Ala Ala Ile Ile Asp	
1265		1270		1275	
His Glu Arg Ile Ala Leu Gly Asn Glu Glu Gly Leu Phe Val Val		His Glu Arg Ile Ala Leu Gly Asn Glu Glu Gly Leu Phe Val Val		His Glu Arg Ile Ala Leu Gly Asn Glu Glu Gly Leu Phe Val Val	
1280		1285		1290	
His Val Thr Lys Asp Glu Ile Ile Arg Val Gly Asp Asn Lys Lys		His Val Thr Lys Asp Glu Ile Ile Arg Val Gly Asp Asn Lys Lys		His Val Thr Lys Asp Glu Ile Ile Arg Val Gly Asp Asn Lys Lys	
1295		1300		1305	
Ile His Gln Ile Glu Leu Ile Pro Asn Asp Gln Leu Val Ala Val		Ile His Gln Ile Glu Leu Ile Pro Asn Asp Gln Leu Val Ala Val		Ile His Gln Ile Glu Leu Ile Pro Asn Asp Gln Leu Val Ala Val	
1310		1315		1320	
Ile Ser Gly Arg Asn Arg His Val Arg Leu Phe Pro Met Ser Ala		Ile Ser Gly Arg Asn Arg His Val Arg Leu Phe Pro Met Ser Ala		Ile Ser Gly Arg Asn Arg His Val Arg Leu Phe Pro Met Ser Ala	
1325		1330		1335	
Leu Asp Gly Arg Glu Thr Asp Phe Tyr Lys Leu Ser Glu Thr Lys		Leu Asp Gly Arg Glu Thr Asp Phe Tyr Lys Leu Ser Glu Thr Lys		Leu Asp Gly Arg Glu Thr Asp Phe Tyr Lys Leu Ser Glu Thr Lys	
1340		1345		1350	
Gly Cys Gln Thr Val Thr Ser Gly Lys Val Arg His Gly Ala Leu		Gly Cys Gln Thr Val Thr Ser Gly Lys Val Arg His Gly Ala Leu		Gly Cys Gln Thr Val Thr Ser Gly Lys Val Arg His Gly Ala Leu	
1355		1360		1365	
Thr Cys Leu Cys Val Ala Met Lys Arg Gln Val Leu Cys Tyr Glu		Thr Cys Leu Cys Val Ala Met Lys Arg Gln Val Leu Cys Tyr Glu		Thr Cys Leu Cys Val Ala Met Lys Arg Gln Val Leu Cys Tyr Glu	
1370		1375		1380	
Leu Phe Gln Ser Lys Thr Arg His Arg Lys Phe Lys Glu Ile Gln		Leu Phe Gln Ser Lys Thr Arg His Arg Lys Phe Lys Glu Ile Gln		Leu Phe Gln Ser Lys Thr Arg His Arg Lys Phe Lys Glu Ile Gln	
1385		1390		1395	
Val Pro Tyr Asn Val Gln Trp Met Ala Ile Phe Ser Glu Gln Leu		Val Pro Tyr Asn Val Gln Trp Met Ala Ile Phe Ser Glu Gln Leu		Val Pro Tyr Asn Val Gln Trp Met Ala Ile Phe Ser Glu Gln Leu	
1400		1405		1410	
Cys Val Gly Phe Gln Ser Gly Phe Leu Arg Tyr Pro Leu Asn Gly		Cys Val Gly Phe Gln Ser Gly Phe Leu Arg Tyr Pro Leu Asn Gly		Cys Val Gly Phe Gln Ser Gly Phe Leu Arg Tyr Pro Leu Asn Gly	
1415		1420		1425	

Glu Gly Asn Pro Tyr Ser Met Leu His Ser Asn Asp His Thr Leu  
 1430 1435 1440  
 Ser Phe Ile Ala His Gln Pro Met Asp Ala Ile Cys Ala Val Glu  
 1445 1450 1455  
 Ile Ser Ser Lys Glu Tyr Leu Leu Cys Phe Asn Ser Ile Gly Ile  
 1460 1465 1470  
 Tyr Thr Asp Cys Gln Gly Arg Arg Ser Arg Gln Gln Glu Leu Met  
 1475 1480 1485  
 Trp Pro Ala Asn Pro Ser Ser Cys Cys Tyr Asn Ala Pro Tyr Leu  
 1490 1495 1500  
 Ser Val Tyr Ser Glu Asn Ala Val Asp Ile Phe Asp Val Asn Ser  
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 Met Glu Trp Ile Gln Thr Leu Pro Leu Lys Lys Val Arg Pro Leu  
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 Asn Asn Glu Gly Ser Leu Asn Leu Leu Gly Leu Glu Thr Ile Arg  
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 1565 1570 1575  
 Ile Asn Asn Lys Arg Arg Tyr Ser Phe Arg Val Pro Glu Glu Glu  
 1580 1585 1590  
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 Gly Ser Ala Leu Lys Arg Glu Phe Ser Gly Gly Ser Tyr Ser Ala  
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 Gly Gly Met Asp Gln Gly Ser Asp Ala Pro Ala Arg Asp Phe Asp  
 1715 1720 1725  
 Gly Glu Asp Ser Asp Ser Pro Arg His Ser Thr Ala Ser Asn Ser  
 1730 1735 1740  
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 Lys Ser Leu Ser Leu Glu Ser Thr Asp Arg Gly Ser Trp Asp Pro  
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&lt;211&gt; 720

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 3566882CD1

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 Phe Thr Arg Asp Asp Phe Glu Gly Asp Trp Arg Leu Val Ala Ser  
 20 25 30  
 Gly Gly Phe Ser Gln Val Phe Gln Ala Arg His Arg Arg Trp Arg

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Thr	Glu	Tyr	Ala	Ile	Lys	Cys	Ala	Pro	Cys	Leu	Pro	Pro	Asp	Ala
				50					55					60
Ala	Arg	Thr	Phe	Ala	Ala	Ser	Val	Ser	Pro	Leu	Pro	Ser	Ile	Tyr
				65					70					75
Leu	Ala	Lys	Ile	Ser	Asp	Phe	Gly	Leu	Ser	Lys	Trp	Met	Glu	Gln
				80					85					90
Ser	Thr	Arg	Met	Gln	Tyr	Ile	Glu	Arg	Ser	Ala	Leu	Arg	Gly	Met
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Leu	Ser	Tyr	Ile	Pro	Pro	Glu	Met	Phe	Leu	Glu	Ser	Asn	Lys	Ala
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Pro	Gly	Pro	Lys	Tyr	Asp	Val	Tyr	Ser	Pro	Pro	Thr	Leu	Pro	Pro
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Arg	Ala	Gly	Val	Ile	Leu	Asp	Val	Gln	Leu	Ser	His	Ser	Glu	Arg
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Val	Leu	Cys	Ile	His	Ser	Phe	Ala	Ile	Val	Ile	Trp	Glu	Leu	Leu
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Thr	Gln	Lys	Lys	Pro	Tyr	Ser	Glu	Leu	Thr	Ser	Gln	Leu	Lys	Glu
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Arg	Lys	Gly	Phe	Asn	Met	Met	Met	Ile	Ile	Ile	Arg	Val	Thr	Ala
				185					190					195
Gly	Met	Arg	Pro	Ser	Leu	Gln	Pro	Val	Ser	Asp	Gln	Trp	Pro	Ser
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Glu	Ala	Gln	Gln	Met	Val	Asp	Leu	Met	Lys	Arg	Cys	Trp	Asp	Gln
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Asp	Pro	Lys	Lys	Arg	Pro	Cys	Phe	Leu	Asp	Ile	Thr	Ile	Glu	Thr
				230					235					240
Asp	Ile	Leu	Leu	Ser	Leu	Leu	Gln	Ser	Arg	Val	Ala	Val	Pro	Glu
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Ser	Lys	Ala	Leu	Ala	Arg	Lys	Val	Ser	Cys	Lys	Leu	Ser	Leu	Arg
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Gln	Pro	Gly	Glu	Val	Asn	Glu	Asp	Ile	Ser	Gln	Glu	Leu	Met	Asp
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Ser	Asp	Ser	Gly	Asn	Tyr	Leu	Lys	Arg	Ala	Leu	Gln	Leu	Ser	Asp
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Arg	Lys	Asn	Leu	Val	Pro	Arg	Asp	Glu	Glu	Leu	Cys	Ile	Tyr	Glu
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Asn	Lys	Val	Thr	Pro	Leu	His	Phe	Leu	Val	Ala	Gln	Gly	Ser	Val
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Gln	Gln	Pro	Asp	Leu	Cys	Ala	Leu	Leu	Leu	Ala	His	Gly	Ala	Asp
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His	Leu	Ala	Ala	Gln	Asn	Asn	Phe	Glu	Asn	Val	Ala	Arg	Leu	Leu
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Arg	Lys	Gln	Gly	Ile	Met	Ser	Phe	Leu	Glu	Gly	Lys	Glu	Pro	Ser	
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&lt;211&gt; 5200

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

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&lt;223&gt; Incyte ID No: 3838946CB1

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&lt;223&gt; Incyte ID No: 72001176CB1

&lt;400&gt; 35

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&lt;223&gt; Incyte ID No: 55064363CB1

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&lt;223&gt; Incyte ID No: 7482044CB1

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&lt;223&gt; Incyte ID No: 7476595CB1

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **KINASES AND PHOSPHATASES SEQUENCES, AND USE THEREOF**

(57) Abstract: The invention provides human kinases and phosphatases (KAP) and polynucleotides which identify and encode KAP. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with aberrant expression of KAP.



WO 02/046384 A3



## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/47431

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/54 C12N15/55 C12N9/12 C07K16/40 C12N9/16  
C12N15/11

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, EPO-Internal, CHEM ABS Data, EMBASE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TOYOOKA SHIN-ICHI ET AL: "HD-PTP: A novel protein tyrosine phosphatase gene on human chromosome 3p21.3." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, 'Online! vol. 278, no. 3, 30 November 2000 (2000-11-30), pages 671-678, XP002216615 ISSN: 0006-291X see Fig. 1 sequence of the full-length HD-PTP which shows 99.94% identity with SEQ ID N 1 of the present application in 1636 amino-acid overlap.	1-10
P, X	& DATABASE SWALL 'Online! 1 March 2001 (2001-03-01) "Protein tyrosine phosphatase HD-PTP" retrieved from EMBL, accession no. Q9H3S7 Database accession no. Q9H3S7 the whole document -/--	1

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance  
 "E" earlier document but published on or after the international filing date  
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)  
 "O" document referring to an oral disclosure, use, exhibition or other means  
 "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  
 "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone  
 "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.  
 "8" document member of the same patent family

Date of the actual completion of the international search

16 October 2002

Date of mailing of the international search report

12.03.03

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/47431

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 00 63392 A (SHIMIZU KENJI ;KYOWA HAKKO KOGYO KK (JP))  26 October 2000 (2000-10-26)  SEQ ID N 1 (claim 4, p58-69) shows 99.9% identity with SEQ ID N 21 of the present application in 1958 nucleot. overlap; SEQ ID N 2 (claim1) shows 99.8% identity with SEQ ID N 1 in 1636 aa overlap</p>	1-13,56
A	<p>GOEKJIAN P G ET AL: "PROTEIN KINASE C IN THE TREATMENT OF DISEASE: SIGNAL TRANSDUCTION PATHWAYS, INHIBITORS, AND AGENTS IN DEVELOPMENT"  CURRENT MEDICINAL CHEMISTRY, BENTHAM SCIENCE PUBLISHERS BV, BE,  vol. 6, no. 9, 1999, pages 877-903,  XP001009989  ISSN: 0929-8673  the whole document</p>	1-20,22, 23,25-95
A	<p>WO 96 13592 A (MANDELKOW ECKHARD ;MANDELKOW EVA MARIA (DE); MAX PLANCK GESELLSCHA) 9 May 1996 (1996-05-09)  the whole document</p>	1-20,22, 23,25-95
A	<p>COHEN PHILIP: "The development and therapeutic potential of protein kinase inhibitors."  CURRENT OPINION IN CHEMICAL BIOLOGY,  vol. 3, no. 4, August 1999 (1999-08),  pages 459-465, XP002216616  ISSN: 1367-5931  the whole document</p>	19,20, 22,23, 25-30
A	<p>SARMIENTO MAURO ET AL: "Structure-based discovery of small molecule inhibitors targeted to protein tyrosine phosphatase 1B."  JOURNAL OF MEDICINAL CHEMISTRY,  vol. 43, no. 2,  27 January 2000 (2000-01-27), pages  146-155, XP002216617  ISSN: 0022-2623  the whole document</p>	19,20, 22,23, 25-30

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 01/47431

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☒ Claims Nos.: 21, 24  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
1-20, 22-23, 25-55 (all partially) and 56, 76 (complete)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box 1.2

Claims Nos.: 21, 24

Present claims 21 and 24 relate to a composition defined by reference to a desirable characteristic or property, namely agonist or antagonist of a polypeptide. The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 84 EPC and / or disclosure within the meaning of Article 83 EPC for none such products. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. A meaningful search could not be carried out for the subject-matter of claims 21 and 24 because it is not possible to determine if any of the presently known substances is falling under the terms of these claims. Besides it is noted, that the compounds of claims 21 and 24 are not rendered novel just because of the fact that they have been identified by the method of claims 20 or 23, e.g. such compounds can already exist. (Apart from this, it is also not possible to establish the scope of these claims without testing all known substances, clearly an undue burden).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-20, 22-23, 25-55 (all partially) and 56,  
76 (complete)

The invention 1 relates to a phosphatase polynucleotide sequence (SEQ ID N 20), its encoded polypeptide (SEQ ID N 1), and their use in the diagnosis, treatment and prevention of diseases and disorders.

2. Claims: 1-20, 22-23, 25-55 (all partially) and 57,  
77 (complete)

The invention 1 relates to a phosphatase or Kinase polynucleotide sequence (SEQ ID N 21), its encoded polypeptide (SEQ ID N 2), and their use in the diagnosis, treatment and prevention of diseases and disorders.

3. Claims: 1-20, 22-23, 25-55 (all partially) and 58,  
78 (complete)

The invention 1 relates to a phosphatase or kinase polynucleotide sequence (SEQ ID N 23), its encoded polypeptide (SEQ ID N 3), and their use in the diagnosis, treatment and prevention of diseases and disorders.

4. Claims: 1-20, 22-23, 25-55 (all partially) and 59,  
79 (complete)

The invention 1 relates to a phosphatase or kinase polynucleotide sequence (SEQ ID N 24), its encoded polypeptide (SEQ ID N 4), and their use in the diagnosis, treatment and prevention of diseases and disorders.

5. Claims: 1-20, 22-23, 25-55 (all partially) and 60,  
80 (complete)

The invention 1 relates to a phosphatase or kinase polynucleotide sequence (SEQ ID N 25), its encoded polypeptide (SEQ ID N 5), and their use in the diagnosis, treatment and prevention of diseases and disorders.

6. Claims: 1-20, 22-23, 25-55 (all partially) and 61,  
81 (complete)

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

The invention 1 relates to a phosphatase or kinase polynucleotide sequence (SEQ ID N 26), its encoded polypeptide (SEQ ID N 6), and their use in the diagnosis, treatment and prevention of diseases and disorders.

7. Claims: 1-20, 22-23, 25-55 (all partially) and 62, 82 (complete)

The invention 1 relates to a phosphatase or kinase polynucleotide sequence (SEQ ID N 27), its encoded polypeptide (SEQ ID N 7), and their use in the diagnosis, treatment and prevention of diseases and disorders.

8. Claims: 1-20, 22-23, 25-55 (all partially) and 63, 83 (complete)

The invention 1 relates to a phosphatase or kinase polynucleotide sequence (SEQ ID N 28), its encoded polypeptide (SEQ ID N 8), and their use in the diagnosis, treatment and prevention of diseases and disorders.

9. Claims: 1-20, 22-23, 25-55 (all partially) and 64, 85 (complete)

The invention 1 relates to a phosphatase or kinase polynucleotide sequence (SEQ ID N 29), its encoded polypeptide (SEQ ID N 9), and their use in the diagnosis, treatment and prevention of diseases and disorders.

10. Claims: 1-20, 22-23, 25-55 (all partially) and 65, 85 (complete)

The invention 1 relates to a phosphatase or kinase polynucleotide sequence (SEQ ID N 30), its encoded polypeptide (SEQ ID N 10), and their use in the diagnosis, treatment and prevention of diseases and disorders.

11. Claims: 1-20, 22-23, 25-55 (all partially) and 66, 86 (complete)

The invention 1 relates to a phosphatase or kinase polynucleotide sequence (SEQ ID N 31), its encoded polypeptide (SEQ ID N 11), and their use in the diagnosis,

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

treatment and prevention of diseases and disorders.

12. Claims: 1-20, 22-23, 25-55 (all partially) and 67,  
87 (complete)

The invention 1 relates to a phosphatase or kinase polynucleotide sequence (SEQ ID N 32), its encoded polypeptide (SEQ ID N 12), and their use in the diagnosis, treatment and prevention of diseases and disorders.

13. Claims: 1-20, 22-23, 25-55 (all partially) and 68,  
88 (complete)

The invention 1 relates to a phosphatase or kinase polynucleotide sequence (SEQ ID N 33), its encoded polypeptide (SEQ ID N 13), and their use in the diagnosis, treatment and prevention of diseases and disorders.

14. Claims: 1-20, 22-23, 25-55 (all partially) and 69,  
89 (complete)

The invention 1 relates to a phosphatase or kinase polynucleotide sequence (SEQ ID N 34), its encoded polypeptide (SEQ ID N 14), and their use in the diagnosis, treatment and prevention of diseases and disorders.

15. Claims: 1-20, 22-23, 25-55 (all partially) and 70,  
90 (complete)

The invention 1 relates to a phosphatase or kinase polynucleotide sequence (SEQ ID N 35), its encoded polypeptide (SEQ ID N 15), and their use in the diagnosis, treatment and prevention of diseases and disorders.

16. Claims: 1-20, 22-23, 25-55 (all partially) and 71,  
91 (complete)

The invention 1 relates to a phosphatase or kinase polynucleotide sequence (SEQ ID N 36), its encoded polypeptide (SEQ ID N 16), and their use in the diagnosis, treatment and prevention of diseases and disorders.

17. Claims: 1-20, 22-23, 25-55 (all partially) and 72,  
92 (complete)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

The invention 1 relates to a phosphatase or kinase polynucleotide sequence (SEQ ID N 37), its encoded polypeptide (SEQ ID N 17), and their use in the diagnosis, treatment and prevention of diseases and disorders.

18. Claims: 1-20, 22-23, 25-55 (all partially) and 73, 93 (complete)

The invention 1 relates to a phosphatase or kinase polynucleotide sequence (SEQ ID N 38), its encoded polypeptide (SEQ ID N 18), and their use in the diagnosis, treatment and prevention of diseases and disorders.

19. Claims: 1-20, 22-23, 25-55 (all partially) and 74, 94 (complete)

The invention 1 relates to a phosphatase or kinase polynucleotide sequence (SEQ ID N 39), its encoded polypeptide (SEQ ID N 19), and their use in the diagnosis, treatment and prevention of diseases and disorders.

20. Claims: 1-20, 22-23, 25-55 (all partially) and 75, 95 (complete)

The invention 1 relates to a phosphatase or kinase polynucleotide sequence (SEQ ID N 40), its encoded polypeptide (SEQ ID N 20), and their use in the diagnosis, treatment and prevention of diseases and disorders.



## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/47431

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0063392 A	26-10-2000	AU 3679400 A WO 0063392 A1	02-11-2000 26-10-2000
WO 9613592 A	09-05-1996	AU 714636 B2 AU 3870295 A CA 2203910 A1 CN 1168699 A WO 9613592 A2 EP 0791067 A2 HU 77081 A2 JP 10508199 T NO 971966 A NZ 295371 A	06-01-2000 23-05-1996 09-05-1996 24-12-1997 09-05-1996 27-08-1997 02-03-1998 18-08-1998 19-06-1997 25-11-1998